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Archives of Internal Medicine

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NORMAL, ABSENT AND PATHOLOGIC TONSILS IN YOUNG WOMEN

A COMPARISON OF HISTORIES *

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BERKELEY, CALIF.

A recent government report [1] estimates that about one third of all operations performed since 1924 among the American urban population were for the removal of tonsils and adenoids. In commenting on this statement, the editor of *The Journal of the American Medical Association* pointed out the urgent need for comprehensive statistical studies of the results of the removal of tonsils to date.[2]

More than one third of the young women entering the University of California during the last ten years had had an operation for the removal of tonsils. As a result of the physical examination required at entrance, about one-third were thought to have normal tonsils; for the remaining one-third, the tonsils were recorded as pathologic, as remnants or as buried or projecting, often without indication of their state of health (table 1).

The opportunity of contrasting the histories of the three groups of women students—those with normal, those with absent and those with pathologic tonsils—gave promise of aiding in the solution of some of the many problems that still surround tonsillectomy.

MATERIAL AND METHOD

The station-to-station method was used for the physical examination required of all students entering the University of California. The histories were taken by nurses, by members of the department of physical education or by older women to whom careful instructions were given. The eyes were examined by an oculist; otorhinologic examinations were made by specialists in that field; the teeth were examined by the dentists of the health service staff, and the general physical examinations were made by physicians. Fortunately, three of the examining physicians have formed the nucleus of the examining staff for the last ten years, thus maintaining a uniformity of standard. It is also fortu-

* Submitted for publication, July 29, 1930.

* Aided by a grant from the Research Board of the University of California.

1. Collins, S. D., and Sydenstricker, E.: An Epidemiological and Statistical Study of Tonsillitis, Pub. Health Bull., 1927, p. 175.

2. Tonsillectomy in the United States, editorial, J. A. M. A. **91**:1195 (Oct. 20) 1928.

nate that the same person has remained the chief of the nose and throat department for this period. Most of the examinations on the nose and throat, however, were made by his associates. The measurements of height, weight, capacity of the chest, estimation of posture and the condition of the feet were made by members of the department of physical education.[3] To make possible the tabulation of all histories and physical observations, the information on the entrance examination cards was transferred to punch cards.

The present study is based on the examinations of 14,000 women students entering the University during the last ten years. It was thought best to confine the study to young white women, so cards of oriental and colored students, of persons over 35 years of age and of those on whom important information was lacking were rejected, leaving 12,530 to be carefully considered.

TABLE 1.—*The Condition of the Tonsils in Relation to Age Incidence*

Condition of Tonsils	15-19 Years		20-24 Years		25-34 Years		15-34 Years	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Normal	2,565	22.23	1,146	36.43	474	33.24	4,185	33.39
Absent	2,756	34.63	914	29.05	464	32.54	4,134	32.99
Pathologic	1,826	22.94	708	22.50	302	21.18	2,836	22.66
Remnants	197	2.48	95	3.02	37	2.59	329	2.62
Buried or projecting	614	7.72	283	9.00	149	10.49	1,046	8.35
Total	7,958	100.00	3,146	100.00	1,426	100.04	12,530	100.01

Accuracy of the Observations and Method.—The accuracy of the original history may well be challenged and no doubt suffers as a result of the haste and excitement of the occasion and through the faulty memories of the students. To obtain some idea of the extent of the error from this source, histories were taken a second time from 250 students when they were at ease and had an abundance of time for reflection. Entrance and second histories agreed in incidence of disease in from 85 to 90 per cent of cases, and as to the age of having the disease, to within one year, in from 65 to 85 per cent of cases. The agreement between the two histories for such indefinite items as the occurrence of headache, discharging ears, common colds, constipation, etc., was less, and was probably influenced by recent experiences. The physical examinations and measurements made at the time of entrance to the University were taken seriously by those who performed and recorded them, and probably are fully as accurate as the records of examinations for the army or for insurance.

The cards were punched in an electrically driven machine with a numbered keyboard. With practice, a careful operator makes few

3. A study of the physical observations of those with normal, absent and pathologic tonsils is in progress.

mistakes, and many of these are quickly discovered in the process of sorting and tabulating. The largest number of errors discovered for one hole was 18 in 12,530 cards, or an error of 0.14 per cent. A larger number may have occurred where they could not be detected, but this does not seem probable. Sorting and tabulating in well adjusted machines should be 100 per cent accurate.

Studies were made: (1) of all cards, according to the condition of the tonsils, for significant facts in the history and physical examination; (2) of the same facts according to the age groups from 15 to 19, from 20 to 24 and from 25 to 34 years; (3) of the group in which the tonsils were absent for the same facts according to the age groups and as related to the age of the patient when the tonsils were removed.

RELATION OF THE CONDITION OF THE TONSILS TO THE INFECTIOUS DISEASES OF CHILDHOOD

Little has appeared in medical literature to show the relationship between the condition of the tonsils and the incidence of the infectious diseases of childhood. In a recent government bulletin, Collins [1] reported data on measles, mumps, whooping cough, chickenpox, scarlet fever and diphtheria in the children of Hagerstown, Md., and found that "in general, the rates are lowest for the normal, slightly higher for the defective, but considerably higher for the removed group." Zahorsky [4] thought that his observations showed that the child beginning his school life without tonsils is in greater danger of acute disease than the child who still has them. Hertz [5] observed 1,185 school children over a period of time and found those with hypertrophied tonsils not any more likely to contract diseases than other children. Crowe, Watkins and Rotholz [6] pointed out the fact that the tonsils are not the only portal of entry and that organisms pass readily through the mucous membrane of the nose and pharynx.

Michailovitz,[7] of Russia, collected data on 1,500 children from 1 to 17 years of age and stated: "The entire absence of scarlet fever among children whose tonsils and adenoids had been removed, and the appearance of scarlet fever among those who had not undergone removal of them, justifies the conclusion that the removal of hypertrophic tonsils

4. Zahorsky: Tonsillectomy in the Young Child, Interstate M. J. **26**:67, 1919.

5. Hertz, P.: Tonsillenhypertrophie bei Schulkindern, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:180, 1928.

6. Crowe, S. J.; Watkins, S. S., and Rothholz, A. S.: Relation of Tonsil and Nasopharyngeal Infection to General Systemic Disorders, Bull. Johns Hopkins Hosp. **28**:1, 1917.

7. Michailovitz, N.: Materialien zum Tonsillarproblem, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **13**:147, 1928-1929.

and adenoids lowers receptivity for scarlet fever." Jordanof,[8] of Münich, employed the data available in the University and two medical clinics to solve the question as to whether or not those who have undergone a tonsillectomy are still subject to scarlet fever. Of 362 for whom a questionnaire was returned, 12, or 3.31 per cent, had had scarlet fever in spite of tonsillectomy. In 8 of the 12, remnants of tonsil tissue remained. In 3 of the 12 cases scarlet fever occurred within a period of 3 weeks after operation and may have been of a traumatic nature. Of 110 patients with scarlet fever only 1 had been operated on for removal of the tonsils; since the disease followed the operation promptly, it may also have been traumatic scarlet fever. Zikowsky,[9] of Vienna, found that among 1,013 patients with scarlet fever only 23 had previously undergone a tonsillectomy. Whether this was due to the fact that persons whose tonsils have been removed are less susceptible to infection with scarlet fever or to the circumstance that only a small percentage of the population of Vienna undergo tonsillectomy could not be ascertained. He considered the tonsils, however, as a portal of entry for scarlet fever, and as a storage room of the virus during the disease. In Kaiser's[10] study of 1,200 tonsillectomized children, the operation was not observed to prevent measles or scarlet fever, but may have lightened the severity of the disease; it seemed, however, to lessen the incidence of diphtheria. In his later publication,[11] he stated that 7.6 per cent of the children whose tonsils had been removed contracted scarlet fever, as against 16 per cent of the control group with tonsils. He thought that children whose tonsils had been removed and in whom scarlet fever developed showed considerably less valvular disease of the heart than those with tonsils who contracted scarlet fever. Bloomfield[12] undertook a statistical study of the triad, scarlet fever, follicular tonsillitis and erysipelas, on the basis of 498 questionnaires. He noted that there is a significant, positive association between the susceptibility to acute follicular tonsillitis and to scarlet fever, but that there is no significant association between the susceptibility to tonsillitis and to diphtheria, or between the susceptibility to scarlet fever and to diphtheria. Doull[13] reported observations on 5,000 white children from

8. Jordanof, K.: Gaumentonsillen und Scharlachinfektion, München. med. Wchnschr. **75**:2172 (Dec. 21) 1928.

9. Zikowsky, J.: Tonsillektomie und Scharlach, Wien. klin. Wchnschr. **42**: 37 (Jan. 10) 1929.

10. Kaiser, A. D.: Incidence of Infection in Tonsillectomized Children, New York State J. Med. **25**:469 (March 20) 1925.

11. Kaiser, A. D.: Incidence of Rheumatism, Chorea and Heart Disease in Tonsillectomized Children, J. A. M. A. **89**:2239 (Dec. 31) 1927.

12. Bloomfield, A. L.: Association of Susceptibility to Scarlet Fever and Acute Tonsillitis, California & West. Med. **28**:477, 1928.

13. Doull, J. A.: Relationship of Tonsillectomy to Occurrence of Scarlet Fever and Diphtheria, Pub. Health Rep. **39**:1833 (Aug. 1) 1924.

5 to 14 years of age, 15 per cent of whom had had their tonsils removed. The observations justified the conclusion that, in the area studied, children whose tonsils had been removed were distinctly less liable to diphtheria, whereas in scarlet fever, no significant difference was shown. Place,[14] who removed tonsils in 122 cases of scarlet fever between the second and the twenty-fourth day of illness, considered tonsillectomy and adenoidectomy as valuable means of shortening the contagiousness of scarlet fever and diphtheria in suitable cases, and that there is reason

TABLE 2.—*The Incidence of Illness as Related to the Condition of the Tonsils*

	Normal		Absent		Patho-logic		Remnants		Buried or Projecting		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Measles	3,622	86.59	3,785	91.56	2,478	87.38	300	91.18	924	88.37	11,109	88.66
Mumps	1,959	46.85	2,192	53.02	1,376	48.51	191	58.05	517	49.43	6,235	49.76
Chickenpox	2,474	59.14	2,680	64.83	1,729	60.97	212	64.44	625	59.75	7,720	61.61
Whooping cough	2,692	64.36	2,817	68.14	1,816	64.03	225	68.39	686	65.58	8,236	65.73
Scarlet fever	567	13.55	658	15.92	380	13.40	44	13.37	134	12.81	1,783	14.21
Typhoid fever	168	4.02	164	3.97	120	4.23	12	3.65	55	5.26	519	4.14
Diphtheria	245	5.86	322	7.79	154	5.43	19	5.78	72	6.88	812	6.48
Malaria	159	3.80	188	4.55	123	4.34	13	3.95	60	5.74	543	4.33
Smallpox	165	3.94	139	3.36	121	4.27	13	3.95	48	4.59	486	3.88
Erysipelas	16	0.38	30	0.72	15	0.53	2	0.60	1	0.01	64	0.51
Pneumonia	432	10.32	533	12.89	264	9.31	41	12.46	108	10.32	1,378	11.00
Pleurisy	115	2.74	174	4.21	78	2.75	6	1.82	23	2.20	396	3.16
Chronic colds	219	5.23	293	7.09	133	4.69	13	3.95	61	5.83	719	5.74
Asthma	19	0.45	60	1.45	23	0.81	4	1.22	7	0.67	113	0.90
Hay-fever	122	2.92	230	5.56	93	3.28	17	5.17	14	1.34	476	3.80
Influenza	1,500	35.84	2,193	53.05	1,179	41.57	172	52.28	415	39.67	5,459	43.57
Rheumatism	126	3.01	289	6.99	85	3.00	18	5.47	41	3.92	559	4.46
Tonsillitis	915	21.86	1,508	36.48	693	24.44	115	34.95	244	23.33	3,475	27.73
Chorea	16	0.28	38	0.92	13	0.46	2	0.61	2	0.19	71	0.57
Otitis media	163	3.89	255	6.17	67	2.36	15	4.56	36	3.44	536	4.28
Boils	266	6.36	290	7.01	201	7.09	13	3.95	74	7.07	844	6.74
Constipation	338	8.07	419	10.14	231	8.14	32	9.73	114	10.90	1,134	9.05
Appendicitis (without operation)	156	3.72	270	6.53	93	3.28	16	4.86	33	3.15	568	4.52
Jaundice	106	2.53	127	3.07	73	2.57	6	1.82	30	2.87	342	2.73
Nephritis	5	0.01	9	0.02	1	0.00	2	0.60	1	0.10	18	0.14
Headache	469	11.20	587	14.20	364	12.83	51	15.50	142	13.58	1,613	12.87
Neurasthenia	92	2.19	87	2.10	31	1.09	3	0.91	20	1.91	233	1.86
Neuritis	22	0.52	63	1.52	23	0.81	6	1.82	9	0.86	123	0.98
Insomnia	44	1.04	57	1.38	20	0.71	3	0.91	9	0.86	133	1.06
Tuberculosis	28	0.67	48	1.16	14	0.49	3	0.91	4	0.38	97	0.77
Total	4,185		4,134		2,836		329		1,046		12,530	

to believe that early operations in scarlet fever tend to reduce the danger of complications. Soto,[15] of Spain, reported that diphtheria occurs in much milder form in those whose tonsils have been removed. Stamberger,[16] of Hungary, followed 100 tonsillectomized patients for from one-half to 3 years after the operation, and came to the conclusion that the tendency to scarlet fever and measles remained stationary, but that the

14. Place, E. H.: Tonsillectomy in the Contagious Diseases, Boston M. & S. J. **187**:434 (Sept. 21) 1922.

15. Soto, E. F.: Indikationen und Kontraindikationen der Mandelexstirpation, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **5**:43, 1924.

16. Stamberger, I.: Ueber die Tonsillenfrage auf Grund von 700 Tonsillektomien, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **10**:386, 1927.

tendency to diphtheria decreased. Schick and Topper [17] found that from 60 to 80 per cent of 100 children gave a positive Schick reaction before removal of the tonsils, and that six months after tonsillectomy only 18 per cent gave a positive reaction. On the basis of these observations they recommended tonsillectomy instead of immunization with toxin-antitoxin for children with diseased tonsils who are sensitive to horse serum, testing children who have been tonsillectomized six months or more previously before giving toxin-antitoxin.

In the present study young women with normal and with pathologic tonsils had had about the same percentage incidence of measles, mumps, chickenpox, whooping cough, scarlet fever and diphtheria (table 2 and

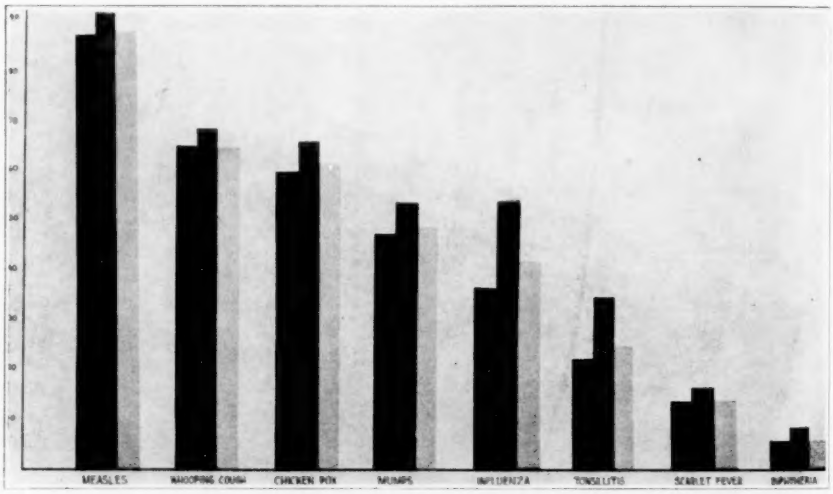

Chart 1.—Incidence of measles, whooping cough, chickenpox, mumps, influenza, tonsillitis, scarlet fever and diphtheria, by groups. Scale indicates per cent. In this and chart 2 the black column indicates the group with normal tonsils, the next column those whose tonsils had been removed, and the third column those with pathologic tonsils.

chart 1). In no instance was the difference between percentages statistically significant (i. e., three times the standard error of difference [18]) (table 3). Those whose tonsils had been removed gave histories showing a higher percentage of all illnesses than did those with

17. Schick, B., and Topper, A.: The Effect of Tonsillectomy on Diphtheria Immunity, Am. J. Dis. Child. **38**:929 (Nov.) 1929.

18. The formula used was:

$$\text{Standard error of difference} = \sqrt{\frac{(\%\text{ of A})\ (100 - \%\text{ of A})}{\text{Number of A}} + \frac{(\%\text{ of B})\ (100 - \%\text{ of B})}{\text{Number of B}}}$$

(Yule: Theory of Statistics, ed. 9, p. 269).

normal, or those with pathologic tonsils (table 2 and chart 1). The differences in percentages were consistent and significant for all of the infectious diseases of childhood (table 4).

TABLE 3.—*Standard Errors of Difference in Percentage Incidence of Disease and Operations in the Groups with Normal and with Pathologic Tonsils*

Disease or Operation	Tonsils Normal, per Cent	Tonsils Pathologic, per Cent	Difference, per Cent	Standard Error of Difference
Measles	86.59	87.38	0.79	±0.82
Mumps	46.85	48.51	1.66	±1.21
Chickenpox	59.14	60.97	1.83	±1.91
Whooping cough	64.36	64.03	0.33	±1.16
Scarlet fever	13.55	13.40	0.15	±0.83
Diphtheria	5.86	5.43	0.43	±0.56
Pneumonia	10.32	9.31	1.01	±0.72
Common colds	5.23	4.69	0.54	±0.53
Influenza	35.84	41.57	5.73*	±1.18
Rheumatism	3.01	3.00	0.01	±0.42
Tonsillitis	21.86	24.44	2.58	±1.02
Chorea	0.28	0.46	0.18	±0.15
Otitis media	3.89	2.36	1.53*	±0.41
History of cardiac disease	3.23	3.02	0.21	±0.43
Damage to mitral valve	2.05	3.42	1.37	±0.41
Damage to aortic valve	0.54	0.83	0.29	±0.20
Appendectomy	4.73	4.48	0.25	±0.51
Nasal operation	2.03	1.23	0.80	±0.30
Operation on cervical glands	0.57	0.99	0.42	±0.22
Mastoid operation	0.76	0.71	0.05	±0.21
Miscellaneous operations	4.78	3.45	1.33	±0.47

* The difference in these percentages is more than three times the standard error and is therefore statistically significant.

TABLE 4.—*Standard Error of Difference in Percentage Incidence of Disease and Operation in the Groups with Normal and with Absent Tonsils*

Disease or Operation	Tonsils Normal, per Cent	Tonsils Absent, per Cent	Difference, per Cent	Standard Error of Difference
Measles	86.59	91.56	4.97*	±0.68
Mumps	46.85	53.02	6.17*	±1.38
Chickenpox	59.14	64.83	5.69*	±1.06
Whooping cough	64.36	68.14	3.78*	±1.03
Scarlet fever	13.55	15.92	2.37*	±0.77
Diphtheria	5.86	7.79	1.93*	±0.55
Pneumonia	10.32	12.89	2.57*	±0.70
Common colds	5.23	7.09	1.86*	±0.53
Influenza	35.84	53.05	17.21*	±1.07
Rheumatism	3.01	6.99	3.98*	±0.48
Tonsillitis	21.86	36.48	14.62*	±0.98
Chorea	0.28	0.92	0.64*	±0.17
Otitis media	3.89	6.17	2.28*	±0.48
History of cardiac disease	3.23	5.10	1.87*	±0.44
Damage to mitral valve	2.05	3.45	1.40*	±0.36
Damage to aortic valve	0.54	0.25	0.29	±0.26
Appendectomy	4.73	10.14	5.41*	±0.57
Nasal operation	2.03	4.67	2.64*	±0.39
Operation on cervical glands	0.57	1.79	1.22*	±0.24
Mastoid operation	0.76	1.96	1.20*	±0.25
Miscellaneous operations	4.78	10.37	5.59*	±0.32

* The difference in these percentages is more than three times the standard error and is therefore statistically significant.

Scarlet fever and diphtheria (table 2 and chart 1) show much the same relationship in frequency in the three groups as do the less serious infectious diseases of childhood, since those whose tonsils had been removed had a significantly higher incidence of infection with scarlet fever and diphtheria than those with normal tonsils (tables 3 and 4).

From a study of those with absent tonsils, by age groups and with relation to the age when the tonsils were removed, evidence seems apparent that the removal of tonsils decreases the incidence of scarlet fever. With the exception of those having their tonsils removed before 5 years of age in the group from 15 to 19 years of age, the earlier the tonsils were removed, the less the total amount of scarlet fever reported (tables 5, 6 and 7 and chart 5). Similar results were not found for measles, mumps, chickenpox or whooping cough, but are found with minor variations and in less degree for diphtheria. It was not found possible to relate these observations to those of other investigators, as data for comparison is limited and as many variations must be taken into account. For instance, records of infections cannot be compared with histories of infections, for obvious reasons. Incidence of infec-

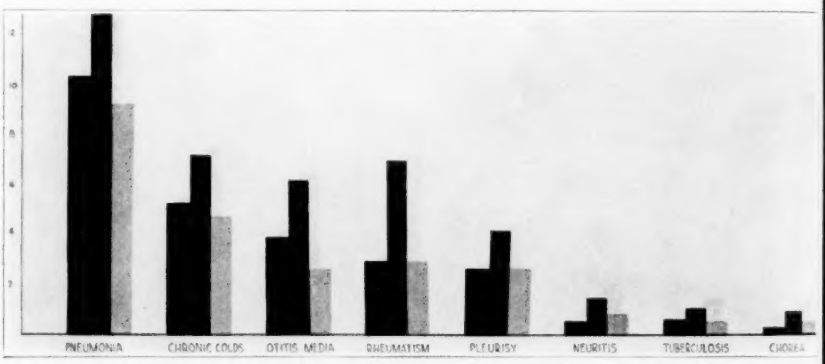

Chart 2.—Incidence of pneumonia, chronic colds, otitis media, rheumatism, pleurisy, neuritis, tuberculosis and chorea, by groups. Scale indicates per cent.

tion in thickly populated places cannot be taken as a standard for incidence in places more sparsely populated. The percentages of those having had infectious diseases considered by ages in this study are, on the whole, less than percentages stated by Collins [19] for the same ages and diseases in Eastern and Middle Western areas.

A reasonable explanation of the higher incidence of infectious disease in the group operated on is that the child who is often ill is finally operated on. The higher incidence of illness would be the indication for a tonsillectomy, rather than the absence of tonsils the cause of more frequent infections. The history of infectious diseases cannot, however, be an influential factor in the removal of tonsils of very young children, since among those whose tonsils were removed before the age of

19. Collins, S. D.: Age Incidence of the Common Communicable Diseases of Children, Pub. Health Bull. **44**:763 (April 5) 1929.

TABLE 5.—*The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 15 to 19 Years as Related to Age of Removal*

Age of removal	0-4 Years				5-9 Years				10-14 Years				15 Years and Over			
Occurrence of disease	Before		After		Before		After		Before		After		Before		After	
Disease	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	21	11.9	141	80.1	408	51.9	393	40.9	756	81.7	95	10.3	340	87.9	9	2.3
Mumps	10	5.7	77	43.8	199	20.7	288	30.0	382	41.3	101	10.9	186	48.1	9	2.3
Chickenpox	13	7.4	105	60.0	329	34.3	309	32.2	559	60.4	70	7.6	241	62.3	2	0.5
Whooping cough	39	22.2	83	47.2	497	51.8	164	17.1	624	67.5	24	2.6	251	64.9	5	1.3
Scarlet fever	2	1.1	22	12.5	50	5.2	61	6.4	108	11.7	29	3.1	59	15.2	1	0.2
Typhoid fever	1	0.6	2	1.1	10	1.0	15	1.6	14	1.5	6	0.6	13	3.4	1	0.2
Diphtheria	3	1.7	6	3.4	29	3.0	17	1.8	51	5.5	16	1.7	28	7.2	1	0.2
Malaria	0	0.0	5	2.8	6	0.6	23	2.4	35	3.8	10	1.1	24	6.2	2	0.5
Smallpox	0	0.0	3	1.7	8	0.8	16	1.7	16	1.7	7	0.7	12	3.1	0	0.0
Erysipelas	1	0.6	1	0.6	2	0.2	4	0.4	4	0.4	4	0.4	2	0.5	0	0.0
Pneumonia	5	2.8	17	9.7	69	7.2	48	5.0	92	9.9	27	2.9	46	11.9	2	0.5
Pleurisy	0	0.0	5	2.8	6	0.6	23	2.4	11	1.2	13	1.4	13	3.4	4	1.0
Chronic colds	2	1.1	9	5.1	22	2.3	46	4.8	22	2.4	27	2.9	21	5.4	14	3.6
Asthma	0	0.0	6	3.4	3	0.3	10	1.0	9	1.0	3	0.3	4	1.0	1	0.3
Hay-fever	3	1.7	11	6.2	3	0.3	37	3.8	10	1.1	35	3.8	9	2.3	12	3.1
Influenza	1	0.6	99	56.2	45	4.7	465	48.4	172	18.6	333	36.0	172	44.4	54	14.0
Rheumatism	1	0.6	4	2.3	8	0.8	16	1.7	28	3.0	20	2.2	12	3.1	8	2.1
Tonsillitis	32	18.2	6	3.4	236	24.6	24	2.5	338	36.5	12	1.3	191	49.4	3	0.8
Chorea	0	0.0	2	1.1	1	0.1	4	0.4	7	0.8	2	0.2	4	1.0	0	0.0
Otitis media	4	2.3	11	6.2	19	2.0	38	4.0	30	3.2	27	2.9	18	4.6	1	0.2
Total number	176		176		960		960		925		925		387		387	

TABLE 6.—*The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 20 to 24 Years as Related to the Age of Removal*

Age of removal	0-4 Years				5-9 Years				10-14 Years				15 Years and Over			
Occurrence of disease	Before		After		Before		After		Before		After		Before		After	
Disease	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	4	18.1	16	72.7	78	48.8	76	47.5	167	78.4	25	11.7	369	89.1	9	2.2
Mumps	1	4.5	10	45.4	32	20.0	54	33.8	92	43.2	23	10.8	229	55.3	6	1.4
Chickenpox	2	9.1	12	54.6	58	36.2	44	27.5	101	47.4	26	12.2	261	63.0	5	1.2
Whooping cough	3	13.6	7	31.8	89	55.6	29	18.1	142	66.7	6	2.8	284	68.6	1	0.2
Scarlet fever	0	0.0	2	9.1	6	3.8	11	6.9	29	13.6	2	0.9	84	20.3	6	1.4
Typhoid fever	0	0.0	3	13.6	4	2.5	7	4.4	7	3.2	2	0.9	19	4.6	0	0.0
Diphtheria	1	4.5	1	4.5	14	8.8	6	3.8	16	7.5	2	0.9	48	11.6	1	0.2
Malaria	0	0.0	0	0.0	1	0.6	3	1.9	3	1.4	3	1.4	20	4.8	3	0.7
Smallpox	0	0.0	1	4.5	2	1.2	1	0.6	8	3.8	2	0.9	18	4.4	4	1.0
Erysipelas	0	0.0	0	0.0	1	0.6	1	0.6	0	0.0	1	0.5	2	0.5	2	0.5
Pneumonia	1	4.5	2	9.1	10	6.3	14	8.8	8	3.8	23	10.8	6	1.5	47	11.4
Pleurisy	1	4.5	0	0.0	9	5.6	0	0.0	5	2.4	3	1.4	6	1.5	16	3.9
Chronic colds	1	4.5	0	0.0	9	5.6	5	3.0	5	2.4	4	1.9	12	2.9	24	5.8
Asthma	0	0.0	0	0.0	4	2.5	2	1.2	1	0.5	2	0.9	2	0.5	3	0.7
Hay-fever	0	0.0	1	4.5	23	14.4	2	1.2	12	5.6	5	2.4	11	2.7	15	3.6
Influenza	11	45.4	1	4.5	71	44.4	5	3.1	72	33.8	22	10.3	64	15.5	164	39.6
Rheumatism	0	0.0	0	0.0	5	3.1	0	0.0	8	3.8	8	3.8	5	1.2	26	6.3
Tonsillitis	1	4.5	2	9.1	14	8.8	42	25.2	3	1.4	72	33.8	2	0.5	232	56.4
Chorea	0	0.0	0	0.0	0	0.0	1	0.6	3	1.4	2	0.9	0	0.0	6	1.4
Otitis media	2	9.1	1	4.5	4	2.5	2	1.2	3	1.4	8	3.8	6	1.4	30	7.2
Total number	22		22		160		160		213		213		414		414	

TABLE 7.—*The Incidence of Disease Before and After Tonsillectomy in the Group Aged from 25 to 34 Years as Related to the Age of Removal*

Age of removal	0-4 Years				5-9 Years				10-14 Years				15 Years and Over			
Occurrence of disease	Before		After		Before		After		Before		After		Before		After	
Disease	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	0	0.0	0	0.0	5	71.4	2	28.6	16	72.7	2	9.1	287	89.4	8	2.5
Mumps	0	0.0	0	0.0	2	28.6	2	28.6	8	36.4	5	22.7	186	57.9	8	2.5
Chickenpox	0	0.0	0	0.0	3	42.8	3	42.8	5	22.7	5	22.7	211	65.7	1	0.3
Whooping cough	0	0.0	0	0.0	3	42.8	0	0.0	6	27.3	4	18.2	206	64.2	2	0.6
Scarlet fever	0	0.0	0	0.0	3	42.8	2	28.6	4	18.2	1	4.5	79	24.6	6	1.9
Typhoid fever	0	0.0	0	0.0	0	0.0	0	0.0	5	22.7	2	9.1	27	8.4	3	0.9
Diphtheria	0	0.0	0	0.0	0	0.0	0	0.0	6	27.3	1	4.5	36	11.2	1	0.3
Malaria	0	0.0	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	15	4.7	2	0.6
Smallpox	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	24	7.5	0	0.0
Erysipelas	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	4	1.2	1	0.3
Pneumonia	0	0.0	0	0.0	0	0.0	0	0.0	1	4.5	5	22.7	42	13.1	3	0.9
Pleurisy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	17	5.3	10	3.1
Chronic colds	0	0.0	0	0.0	0	0.0	0	0.0	1	4.5	1	4.5	20	6.2	8	2.5
Asthma	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.3	3	0.9
Hay-fever	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	4.5	10	3.1	6	1.9
Influenza	0	0.0	0	0.0	0	0.0	3	42.8	1	4.5	6	27.3	111	34.6	67	20.9
Rheumatism	0	0.0	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	27	8.4	6	1.9
Tonsillitis	0	0.0	0	0.0	0	0.0	1	14.3	9	40.9	1	4.5	162	50.5	5	1.6
Chorea	0	0.0	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	1	0.3	0	0.0
Otitis media	0	0.0	0	0.0	0	0.0	1	14.3	2	9.1	1	4.5	18	5.6	3	0.9
Total number	0		0		7		7		22		22		321		321	

TABLE 8.—*Normal Tonsils: History of Illness by Age Groups*

	15-19 Years		20-24 Years		25-34 Years		15-34 Years	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	2,168	84.52	1,023	89.27	431	90.93	3,622	86.59
Mumps	1,117	43.55	571	49.82	271	57.17	1,959	46.85
Chickenpox	1,504	58.64	682	59.51	288	60.76	2,474	59.14
Whooping cough	1,642	64.02	740	64.57	310	65.40	2,692	64.36
Scarlet fever	284	11.07	179	15.62	104	21.94	567	13.55
Typhoid fever	70	2.73	61	5.32	37	7.81	168	4.02
Diphtheria	122	4.76	84	7.33	39	8.23	245	5.86
Malaria	87	3.39	49	4.28	23	4.85	159	3.80
Smallpox	82	3.20	60	5.24	23	4.85	165	3.94
Erysipelas	9	0.35	2	0.17	5	1.05	16	0.38
Pneumonia	238	9.28	129	11.25	65	13.71	432	10.32
Pleurisy	47	1.83	32	2.79	36	7.59	115	2.74
Chronic colds	125	4.87	67	5.85	27	5.70	219	5.23
Asthma	9	0.35	6	0.52	4	0.84	19	0.45
Hay-fever	63	2.46	38	3.32	21	4.43	122	2.92
Influenza	891	34.73	422	36.82	187	39.45	1,500	35.84
Rheumatism	68	2.65	38	3.32	20	4.22	126	3.01
Tonsillitis	495	19.30	289	25.22	131	27.64	915	21.86
Chorea	9	0.35	3	0.26	4	0.84	16	0.38
Otitis media	93	3.62	48	4.19	22	4.64	163	3.89
Boils	168	6.55	64	5.58	34	7.17	266	6.36
Constipation	159	6.20	107	9.34	72	15.19	338	8.07
Appendicitis	73	2.85	58	5.06	25	5.27	156	3.72
Jaundice	54	2.11	30	2.62	22	4.64	106	2.53
Nephritis	4	0.16	1	0.09	0	0.00	5	0.01
Headaches	292	11.38	127	11.08	50	10.55	469	11.20
Neurasthenia	37	1.44	29	2.53	26	5.48	92	2.19
Neuritis	7	0.27	6	0.52	9	1.90	22	0.52
Insomnia	11	0.43	20	1.74	13	2.74	44	1.04
Tuberculosis	10	0.39	9	0.78	9	1.90	28	0.67
Total	2,565		1,146		474		4,185	

TABLE 9.—*Absent Tonsils: History of Illness by Age Groups*

	15-19 Years		20-24 Years		25-34 Years		15-34 Years	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	2,529	91.76	832	91.03	424	91.38	3,785	91.56
Mumps	1,412	51.23	513	56.13	267	57.54	2,192	53.02
Chickenpox	1,819	66.00	568	62.14	293	63.15	2,680	64.83
Whooping cough	1,901	68.98	625	68.38	291	62.72	2,817	68.14
Scarlet fever	377	13.68	161	17.61	120	25.86	658	15.92
Typhoid fever	71	2.58	44	4.81	49	10.56	164	3.97
Diphtheria	171	6.20	101	11.05	50	10.78	322	7.79
Malaria	123	4.46	37	4.05	28	6.03	188	4.55
Smallpox	69	2.50	42	4.60	28	6.03	139	3.36
Erysipelas	18	0.65	7	0.76	5	1.08	30	0.72
Pneumonia	340	12.34	124	13.57	69	14.87	533	12.89
Pleurisy	89	3.23	44	4.81	41	8.84	174	4.21
Chronic colds	178	6.46	68	7.44	47	10.13	293	7.09
Asthma	39	1.42	15	1.64	6	1.29	60	1.45
Hay-fever	133	4.82	73	7.99	24	5.17	230	5.56
Influenza	1,486	53.92	460	50.33	247	53.23	2,193	53.05
Rheumatism	112	4.06	60	6.56	46	9.91	289	6.99
Tonsillitis	893	32.40	388	42.45	227	48.92	1,508	36.48
Chorea	23	0.83	13	1.42	2	0.43	38	0.92
Otitis media	164	5.95	59	6.46	32	6.90	255	6.17
Boils	191	6.93	58	6.34	41	8.84	290	7.01
Constipation	219	7.95	119	13.12	81	17.46	419	10.14
Appendicitis	159	5.77	68	7.44	43	9.27	270	6.53
Jaundice	75	2.72	31	3.39	21	4.52	127	3.07
Nephritis	4	0.14	2	0.22	3	0.65	9	0.02
Headaches	396	14.37	128	14.00	63	13.58	587	14.20
Neurasthenia	43	1.56	26	2.84	18	3.88	87	2.10
Neuritis	24	0.87	20	2.19	19	4.09	63	1.52
Insomnia	18	0.65	19	2.08	20	4.31	57	1.38
Tuberculosis	24	0.87	11	1.20	13	2.80	48	1.16
Total	2,756		914		464		4,134	

5 years in the group from 15 to 19 years of age (tables 5, 6 and 7 and chart 5), considerably more than 50 per cent had not had measles, mumps, chickenpox or whooping cough before operation. When the factors of age and epidemic cycles are taken into account as much as is possible by considering the persons in age groups, the same general greater incidence of infectious disease in the absent tonsil group is apparent (tables 8, 9 and 10 and chart 3). A study of whether the infection preceded or followed the tonsillectomy should prove helpful,

TABLE 10.—*Pathologic Tonsils: History of Illness by Age Groups*

	15-19 Years		20-24 Years		25-34 Years		15-34 Years	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Measles	1,576	86.31	631	89.12	271	88.74	2,478	87.38
Mumps	855	46.82	361	50.99	160	52.98	1,376	48.51
Chickenpox	1,124	61.56	424	59.89	181	59.93	1,729	60.97
Whooping cough	1,162	63.64	470	66.38	184	60.93	1,816	64.03
Scarlet fever	215	11.77	111	15.68	54	17.88	380	13.40
Typhoid fever	55	3.01	30	4.24	35	11.59	120	4.23
Diphtheria	97	5.31	40	5.65	17	5.63	154	5.43
Malaria	76	4.16	23	3.25	24	7.95	123	4.34
Smallpox	70	3.83	32	4.52	19	6.29	121	4.27
Erysipelas	7	0.38	4	0.56	4	1.32	15	0.53
Pneumonia	156	8.54	71	10.03	37	12.25	264	9.31
Pleurisy	40	2.19	20	2.82	18	5.96	78	2.75
Chronic colds	72	3.94	42	5.93	19	6.29	133	4.69
Asthma	16	0.88	6	0.85	1	0.33	23	0.81
Hay-fever	58	3.18	25	3.53	10	3.31	93	3.28
Influenza	750	41.07	305	43.08	124	41.06	1,179	41.57
Rheumatism	47	2.57	25	3.53	13	4.30	85	3.00
Tonsillitis	437	23.93	174	24.58	82	27.15	693	24.44
Chorea	5	0.27	6	0.85	2	0.66	13	0.46
Otitis media	34	1.86	23	3.25	10	3.31	67	2.36
Boils	127	6.96	50	7.06	24	7.95	201	7.09
Constipation	129	7.06	64	9.04	38	12.58	231	8.14
Appendicitis	50	2.74	28	3.94	15	4.97	93	3.28
Jaundice	42	2.30	17	2.40	14	4.64	73	2.57
Nephritis	1	0.05	0	0.00	0	0.00	1	0.04
Headaches	241	13.20	88	12.43	35	11.59	364	12.83
Neurasthenia	12	0.66	11	1.55	8	2.65	31	1.09
Neuritis	12	0.66	6	0.85	5	1.66	23	0.81
Insomnia	2	0.11	5	0.71	13	4.30	20	0.71
Tuberculosis	5	0.27	6	0.85	3	0.99	14	0.49
Total	1,826		708		302		2,836	

but fails in much of its purpose, as no figures have been found with which satisfactory comparisons can be made, despite the abundant information of the recent government report [19] on the age incidence of communicable diseases.

There seems to be no general agreement as yet as to the effect of the condition of the tonsils on the incidence of the infectious diseases of childhood. The literature is contradictory and confusing. If the explanation that the child who is often ill ultimately has his tonsils removed is accepted for the slightly higher percentages of all illnesses in the group with absent tonsils, the present study does not necessarily indicate an interdependent relationship between the condition of the tonsils and the percentage of incidence of measles, mumps, whooping cough and chickenpox. However, there seems to be a slightly beneficial effect of

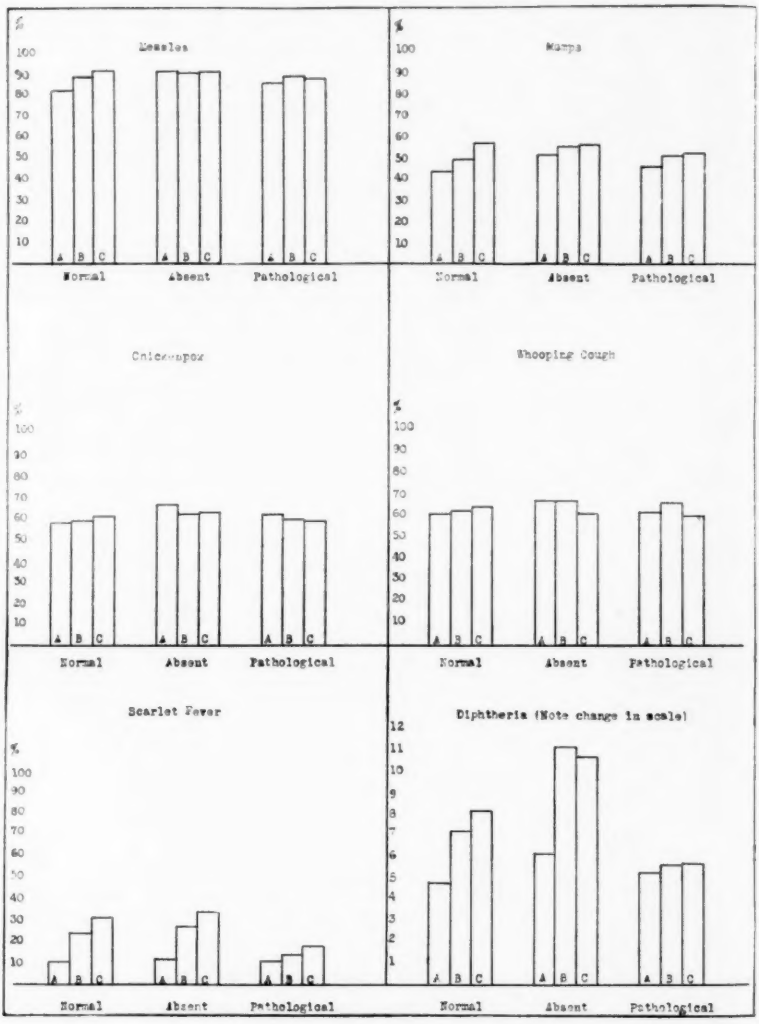

Chart 3.—Incidence of infectious diseases according to age and the condition of the tonsils. In this and chart 4, *A* indicates the group from 15 to 19 years (2,565 with normal tonsils, 2,756 whose tonsils had been removed and 1,826 with pathologic tonsils); *B*, those from 20 to 24 years (1,146 with normal tonsils, 914 whose tonsils had been removed and 708 with pathologic tonsils); *C*, those from 25 to 34 years (476 with normal tonsils, 464 whose tonsils had been removed and 302 with pathologic tonsils).

early tonsillectomy on the susceptibility to scarlet fever and to diphtheria. The last mentioned point needs confirmation from larger groups of subjects before its final acceptance.

RELATION TO DISEASES OF THE RESPIRATORY TRACT

As a result of a questionnaire study of 529 persons who had had their tonsils removed, Coakley and Pratt [20] thought that a well performed tonsillectomy and adenoidectomy caused a marked lessening of the acute infections of the upper respiratory tract. Soto [15] stated that tonsillectomized children are less subject to catarrhal or general infections than children with tonsils. Treen [21] advocated the removal of tonsils for "recurrent catarrh of the nose and throat." Although Stoker [22] raised an objection to the removal of normal tonsils, he advises their removal for chronic rhinitis or sinusitis and for repeated colds and sore throats. Pond [23] discussed the possibility of infected tonsils causing sinusitis, and of sinusitis resulting in tonsillitis, and gave figures to show that "tonsillectomy in adults does cure a few infected sinuses, and improves many." Kaiser [10] followed 1,200 children for a period of 3 years after tonsillectomy, and found that the operation did not influence infections of the larynx, bronchi and lungs. However, in a second article,[11] contrasting the 1,200 children operated on with 1,200 for whom the operation was advised but not performed, he stated: "Frequent head colds relieved in 75 per cent of the cases offers a definite cause for the removal of tonsils and adenoids." In reviewing histories of 12,000 colds in 5,000 Yale students, Smiley [24] stated: "Since removal of nasal obstructions and diseased tonsils in more than half of those having 'four or more' colds a year has not resulted in a reduction of the frequent colds, it seems fair to conclude that nasal obstructions and diseased tonsils are not major factors in the majority of persons suffering with frequent colds." Forsythe [25] found for 537 "students of the University of Michigan who had had their tonsils removed 40 per cent more acute respiratory infections than for those who have not been

20. Coakley, C. G., and Pratt, E. L.: Analysis of the Systemic and Local Conditions Following Tonsillectomy and Adenoidectomy, Laryngoscope **32**:82, 1922.

21. Treen, Jozsef: Ueber das Tonsillenproblem und die Bakterieninvasion ueber die Luftwege, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:180, 1928.

22. Stoker, Fred: The "Tonsil" Question, Lancet **2**:1125 (Nov. 26) 1927.

23. Pond, C. W.: Some End Results of Tonsillectomy, with Special Reference to Sinus Infection in Adults, Laryngoscope **40**:286, 1930.

24. Smiley, D. F.: A Study of the Acute Infections of the Throat and Respiratory System, J. A. M. A. **82**:540 (Feb. 16) 1924.

25. Forsythe, W. E.: Health Record of University Students as Related to Tonsillectomy, Pub. Health Rep. **43**:560 (March 9) 1928.

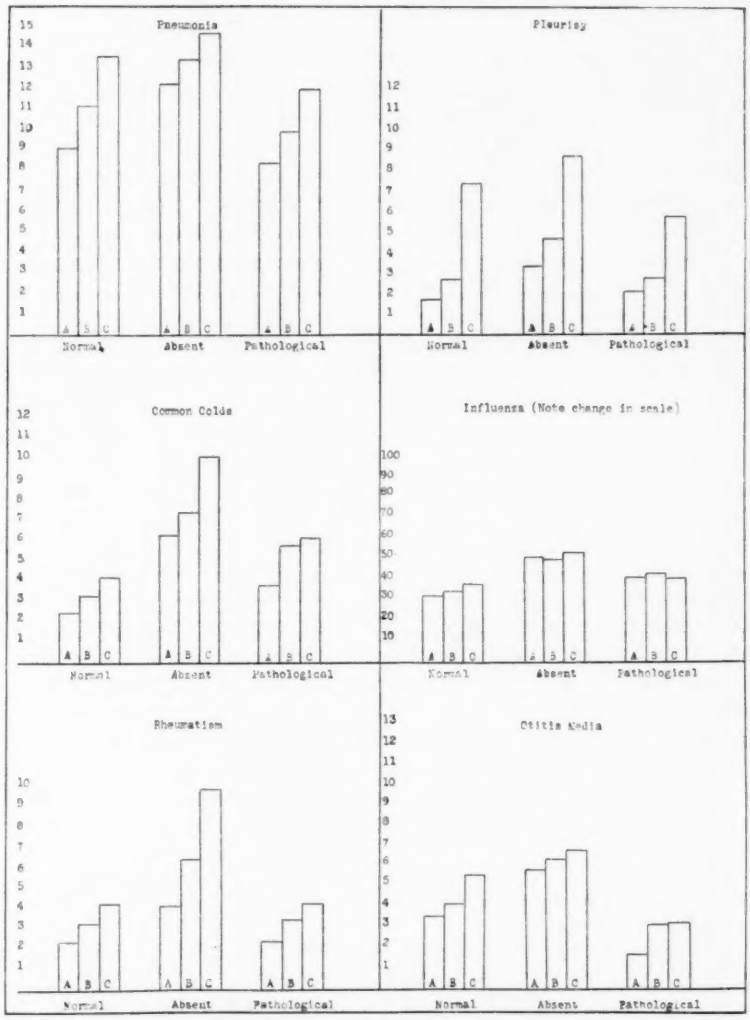

Chart 4.—Incidence of infections of the respiratory tract, according to age and the condition of the tonsils.

favored with the surgeon's knife." Norsk [26] observed that when catching a cold after a tonsillectomy patients seem to be subject to attacks of acute pharyngitis, and he suspected that this tendency may have been present before operation and its symptoms obscured by the far more serious ones pertaining to tonsillitis.

The incidence of pneumonia, pleurisy, chronic colds and tuberculosis differs only slightly in the normal tonsil and pathologic tonsil groups, while their incidence is greater among those whose tonsils had been removed than among those of the other two groups (tables 2, 3 and 4 and chart 2). Here, as well as in the case of infectious diseases of childhood, the observations remain consistent when considered by age groups (tables 8, 9 and 10 and chart 4). Probably the same explanation holds for the slightly greater frequency of the history of respiratory illness as for the greater frequency of infectious diseases in the absent tonsil group. The child who is often ill is apt ultimately to be operated on.

The answer to the question, "Are you subject to colds?" would, in most instances, be answered on the basis of recent experience and would seem to indicate that the removal of tonsils is not an entirely satisfactory method of preventing infections of the upper respiratory tract, since 7.09 per cent of those whose tonsils had been removed gave a history of frequent colds and only 5.23 per cent of those with normal tonsils and 4.69 per cent of those with pathologic tonsils gave a similar history. According to these figures, there is little argument for removing pathologic tonsils to lessen the incidence of the ordinary infections of the respiratory tract, since the subjects with pathologic tonsils had fewest colds. There is, however, more chance than reliability in the slight difference in percentages between those with normal, and those with pathologic tonsils.

In the literature there is much the same contradiction and confusion relative to the effect of the condition of the tonsils on the occurrence of infection of the respiratory tract as on the frequency of infectious diseases of childhood. If the explanation that the child with many infections of the respiratory tract ultimately has his tonsils removed is accepted to account for the universally higher percentage of infections of the respiratory tract in the group whose tonsils are absent than in the group with normal tonsils or the group with pathologic tonsil, this study shows no significant relationship between the condition of the tonsils and the incidence of infections of the respiratory tract.

Local infections of the tonsillar tissue, with or without peritonsillar abscess or hyperplasia of Waldeyer's ring, interfering with deglutition or respiration, undoubtedly furnished the indication for operations on

26. Norsk, Frans: Ergebnisse der Tonsillektomie bei Erwachsenen, Ztschr. f. Hals-, Nasen- u. Ohrenh. **2**:294, 1922.

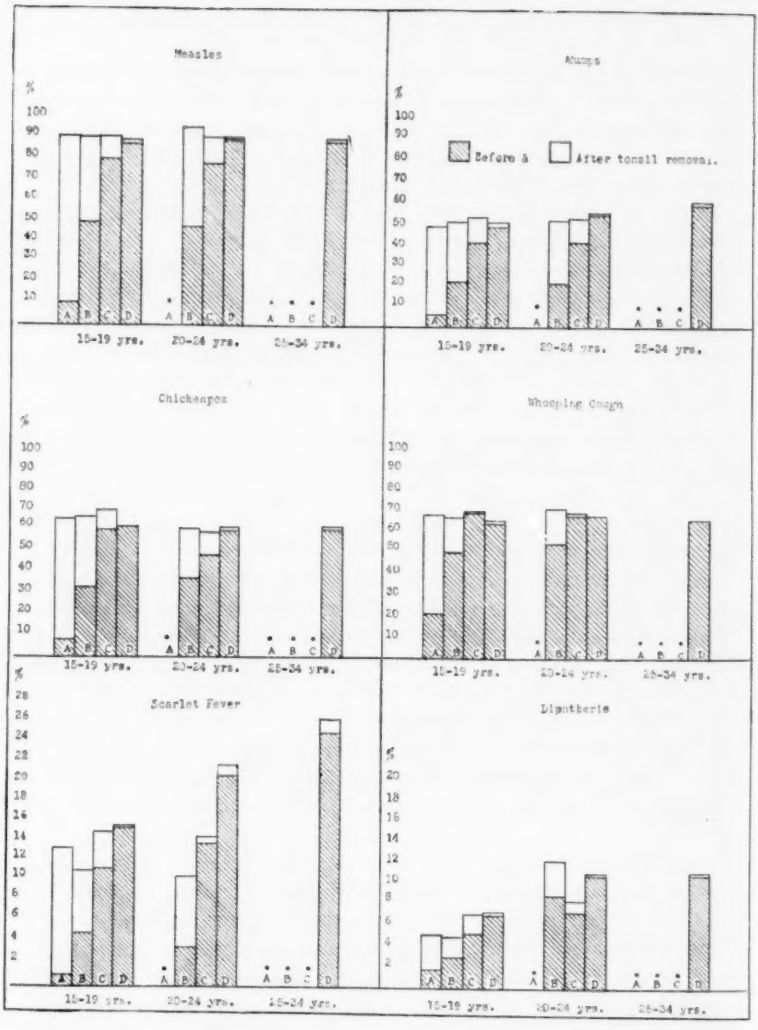

Chart 5.—Incidence of infectious diseases before and after tonsillectomy, according to age and the year when the tonsils were removed. In this and chart 6, *A* indicates those whose tonsils were removed before 5 years of age (176 in the 15 to 19 age group, 22 in the 20 to 24 age group and 0 in the 25 to 34 age group); *B*, those whose tonsils were removed between 5 and 10 years of age (960 in the 15 to 19 age group, 160 in the 20 to 24 age group and 7 in the 25 to 34 age group); *C*, those whose tonsils were removed between 10 and 15 years of age (925 in the 15 to 19 age group, 213 in the 20 to 24 age group and 22 in the 25 to 34 age group); *D*, those whose tonsils were removed after 15 years of age (387 in the 15 to 19 age group, 414 in the 20 to 24 age group and 321 in the 25 to 34 age group). The asterisks indicate that the data were insufficient to justify graphic representation.

the tonsils in early times. That operation for the removal of tonsillar tissue ranks with the oldest of operations and has been practiced throughout the ages is evident by the fact that Hindu physicians [27] advocated the removal of the tonsils as early as 1000 B. C., advising that they be seized with forceps and cut with a semicircular knife. Hippocrates advised opening tonsillar abscesses, but did not speak of removal of the tonsils. Celsus probably initiated finger dissection, as he suggested that tonsils that remain indurated after inflammation be disengaged all around with the finger and pulled out. Galen described a snare for amputation, and some mention of the operation sounds as if it were an ordinary practice of his day. Peter Lowe, founder of the School of Medicine of Glasgow, published a book in 1634 in which he described: (1) opening tonsillar abscesses, (2) tracheotomy for suffocation from enlarged tonsils, (3) removal of tonsils by snare, (4) by cautery and (5) by pulling away with crossets.

Wiseman [28] described removal of the tonsils by making a ligature about their base and snipping them off with a pair of crooked probe scissors.

The remarks of Samuel Sharp,[29] surgeon at Guy's Hospital from 1733 to 1757, on removal of the tonsils are quaint and worthy of repetition, since they contain some elements of thought that have long occupied the minds of physicians, and hint at others that are under discussion at the present moment:

> Besides there is no operation in surgery that, in my opinion, ought to give an operator so much encouragement. It is neither dreadful in the doing nor melancholy in the event. . . . The patient has always been restored to a perfect and lasting health.
>
> The continued good success attending this operation is an answer to the common objection that has formerly been made to it, and perhaps may still be an objection with some foreigners, that it must be dangerous to destroy a part by which nature has been accustomed to fling off any disorder of the constitution, left for want of a discharge, the humour continuing to (circulate) float in the blood, should produce a fever or some other ill habit of the body. It was thought that the frequent accidental inflammation of scirrhous tonsils are not to be considered as local disorders, but like the gout, a distemper in the constitution, which must be received on some one part for the good of the whole. However, the absolute exemption from future inflammatory disorders, in consequence of the operation, seems to demonstrate that the weakness of the part is the chief cause of the complaints.

Local infections of tonsillar tissue, with or without tonsillar abscess, continue to be listed and generally accepted as indications for removal

27. Mollison, W. M.: Work of Samuel Sharp and His Predecessors on Function and Surgery of Tonsils, Guy's Hosp. Rep. **78**:93, 1928.

28. Wiseman, Richard: Severall Chirurgicall Treatises, ed. 5, London, B. Tooke, 1719.

29. Sharp, Samuel: Critical Enquiry into the Present State of Surgery, London, J. & R. Torsin, 1750.

of the tonsils. On this point there seems to be little argument when relief of the local condition is the object of the operation.

Almost 28 per cent of all students entering the University of California gave a history of having had tonsillitis (table 2). The difference between the percentage of those with normal tonsils giving a history of tonsillitis and those with pathologic tonsils giving a similar history is less than might be expected. There were 21.86 per cent of the former and 24.44 per cent of the latter, with a difference of only 2.58 per cent ± 1.02. The difference between the percentage of those whose tonsils had been removed (36.48 per cent) and those with normal tonsils (21.86 per cent) giving a history of tonsillitis is, in contrast, considerable: 14.62 per cent ± 0.98. It is not surprising that those whose tonsils had been removed gave a history of an attack of tonsillitis since the local inflammation of the tissue, especially if recurrent, is considered by most physicians a definite indication for its removal.

RELATIONS TO OTITIS MEDIA

Many textbooks influential in shaping the opinions of members of the medical profession give recurrent infections of the ear, or chronic aural discharge as a definite indication for tonsillectomy. Some recommend the operation as a prophylactic measure against otitis media. Crowe, Watkins and Rothholz,[6] basing their conclusions on 1,000 cases of tonsillectomy at Johns Hopkins Hospital during the 5 years preceding 1917, gave otitis media and eustachian salpingitis as indications for tonsillectomy. Rojas,[30] of Spain, found 44 per cent of 4,266 school children with enlarged tonsils and a diminution in hearing. Eight months after tonsillectomy, only 12 per cent remained hard of hearing. Treen,[21] of Hungary, advised tonsillectomy for recurrent infection of the middle ear. Van der Hoeven,[31] of Holland, considered that improvement occurred in 80 per cent of 902 patients operated on for removal of the tonsils, including 42 patients with infection of the middle ear. Kaiser[11] followed 1,200 children for 3 years after tonsillectomy, and stated that the operation lessened the chances of a discharge from the ear. Cummings[32] gave deafness in children and chronic aural discharge as indications for tonsillectomy. Love,[33] basing his judgment on 4,000 patients operated on, considered both deafness and a discharge

30. Rojas, F. A.: Mandelhypertrophie und Adenoide in der Schule, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:755, 1928.

31. van der Hoeven, L. J.: Bemerkungen im Anschluss an 3,300 Halsoperationen bei Kindern, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **7**:231, 1925.

32. Cummings, G. O.: Why Remove Tonsils and Adenoids? M. J. & Rec. **128**:201 (Sept. 5) 1928.

33. Love, J. K.: Tonsillectomy in School Clinics, J. Laryng. & Otol. **39**:135, 1924.

from the middle ear as arguments for removal of the tonsils. Wagers [34] followed 247 patients after removal of the tonsils, and in conclusion considered aural discharge an indication for operation. Stoker,[22] although warning against needless operation, included suppuration of the ears as an indication. Ingersoll [35] reported on a survey of the school children of Rochester, N. Y., in which 23,000 of 58,000 were listed as having markedly hypertrophied or badly infected tonsils slated for removal. As a result of the campaign, 8,000 children between the ages of 2 and 16 had tonsils removed during a period of 3 months. Following the operations there were 30 cases of acute purulent otitis media, none of which went on to mastoiditis. Collins [1] found diseases of the ear lowest among children with normal tonsils, higher among those with defective tonsils and highest among those whose tonsils had been removed. Paton,[36] of England, in considering the histories and observations of 424 girls between the ages of 13 and 15 years found that children operated on not only are not benefited but, on the contrary, are in worse condition and that removal of the tonsils and adenoids causes a more frequent appearance of running ears than in the control group.

Since otitis media is commonly considered as an urgent indication for the removal of tonsils, it is not surprising to find that a large number of those whose tonsils were absent had a history of aural infection (table 2 and chart 2). No doubt, in many instances the aural infection preceded the removal of the tonsils. The presence of pathologic tonsils does not seem to predispose a patient to aural infection since those with normal tonsils had a significantly higher percentage of otitis media than those with pathologic tonsils (tables 3 and 4). When one considers the number of cases of disease of the ear preceding and following tonsillectomy at various ages (table 5), the arguments in favor of removing the tonsils as a prophylaxis against aural infection are not convincing. In the group from 15 to 19 years of age the earlier the tonsils were removed the higher was the total incidence of otitis media. In the group from 20 to 24 years of age the relation of the age of operation to the total number of cases of otitis media is reversed; the earlier the operation, the less the total involvement of the ear. The fact that half the cases of aural infection followed, rather than preceded, tonsillectomy in the groups from 15 to 19 and from 20 to 24, years of age when the tonsils were removed

34. Wagers, A. J.: Study of Post-Tonsillectomized Individuals, Laryngoscope **31**:310, 1929.

35. Ingersoll, E. S.: Surgical Study of 8,000 Tonsillectomies in Children, Tr. Sect. Laryng., Otol. & Rhin., A. M. A., 1926, p. 142.

36. Paton, J. H. P.: Tonsil-Adenoid Operation and Some of Its Results, Quart. J. Med. **22**:107, 1928.

before the age of 10 years is interesting and indicates that removal of the tonsils is not an effective means of avoiding otitis media.

Neither the literature on the relation of otitis media to the condition of the tonsils nor the results of the present study furnish conclusive proof of the existence of a causal relationship between the tonsils and infections of the ear.

RELATION TO RHEUMATISM AND ARTHRITIS

The literature on the relation of the condition of the tonsils to rheumatism and arthritis is so voluminous as to be impossible of citation. Only outstanding contributions, reports of research councils, a few observations of investigators in foreign countries and the recent literature can be reviewed.

The majority of textbooks, both those dealing with conditions of the nose and throat and those dealing with general medicine emphasize the association of tonsillitis and diseases of the joints, and many advocate tonsillectomy as a cure or prophylaxis for arthritis and acute rheumatic fever. Some are emphatic in their attitudes; e. g., Tilly,[37] who included rheumatism and articular inflammations as indications for tonsillectomy, concluded by saying: "It is reasonable to believe that the functions of the tonsils are of little importance, while their possibilities for evil when the balance between protection and invasion has been overcome are scarcely capable of exaggeration."

James Harper,[38] surgeon of diseases of the nose, throat and ear at the Royal Infirmary, Glasgow, after discussing possible functions of the tonsils, defended the practice of removing them "should there be any reason to suspect them of having an ill effect on the well being of the individual"; he considered rheumatism as a definite indication for the operation. Kaiser[10] gave the presence of positive or suspected evidence of the rheumatic syndrome—rheumatism, chorea, heart disease—as a definite indication for tonsillectomy, in view of the lessened incidence of heart disease in the group operated on. In a second article,[11] however, in which he reviewed the histories and observations on 1,200 children presenting all or part of the rheumatic syndrome, among the 48,000 children included in the total survey, he said: "Rheumatic fever, joint pain or growing pains occurred in both groups; 8 per cent in the tonsillectomized group, and 10 per cent in the nontonsillectomized group. Many of the former had had rheumatic symptoms before tonsillectomy. The tonsillectomized child not yet infected has a decidedly better chance to escape rheumatic infection over the same period of time than the child

37. Tilly, Herbert: Diseases of the Nose and Throat, ed. 4, London, H. K. Lewis & Company, 1919, p. 400.

38. Harper, James: The Tonsil and Its Function, Glasgow M. J. **94**:344, 1920.

whose tonsils have not yet been removed. Recurrent attacks of rheumatic fever were less common in the groups in which operations had been performed."

Findlay, Macfarlane and Stevenson [39] thought that in the case of rheumatic manifestations characterized by arthritis the evidence in favor of the beneficial effect of tonsillectomy is slight. Robey [40] advocated removal of the tonsils during the active stage of rheumatic fever. The earlier the focus is discovered and removed, the more hope one has of lessening recurrences and the danger of cardiac involvement. In several cases in which symptoms recurred repeatedly he considered that the results of operation had been brilliant. Bertoin,[41] of France, considered that extirpation is indicated in recurring inflammatory rheumatism if other sources of infection cannot be determined. When done in time, it may prevent serious diseases of the organism. After the appearance of these diseases, however, tonsillectomy is of no benefit and therefore, is not indicated. Wein,[42] of Hungary, drew the following conclusion from 2,500 extirpations: Polyarthritis, acute glomerular nephritis and incipient endocarditis are frequently influenced favorably by tonsillectomy. Key-Aberg,[43] of Sweden, advocated that in every case, or at least in every recidivous case, in which practical experience has taught that the complaint may have originated in the tonsils, such as diseases of the kidneys and inflammatory rheumatism, the tonsils should be removed. The absence of visible pathologic changes of the tonsils does not offer a definite contraindication, considering the vital and social dangers of the diseases. Wodak,[44] of Czechoslovakia, included under strict indications for tonsillectomy, inflammatory rheumatism, other rheumatic processes, endocarditis and nephritis occurring one or more times after angina, so that their connection with the tonsils is established. Rosselli,[45] of Italy, favored the total removal of tonsils for the generally known and acknowledged indications:

39. Findlay, L.; Macfarlane, J. W., and Stevenson, M. M.: Tonsillectomy in Prevention and Treatment of Rheumatism, Arch. Dis. Childhood **4**:313, 1929.

40. Robey, W., and Finland, M.: The Effect of Tonsillectomy on the Acute Attack of Rheumatic Fever; Preliminary Report, Arch. Int. Med. **45**:772 (May) 1930.

41. Bertoin, Roger: Indications du traitement amygdalien dans le rhumatisme, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **8**:335, 1925-1926.

42. Wein, Zoltan: Der gegenwärtige Stand der Frage der Mandeloperationen, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **8**:727, 1925-1926.

43. Key-Aberg, Hans: Ueber Tonsillektomie, besonders bei Kindern, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **10**:841, 1927.

44. Wodak, E.: Einige Bemerkungen über Tonsillektomie, Med. Klin. **24**:807 (May 25) 1928.

45. Rosselli, Sanvenero: La tonsillectomania totale: Indicazioni e technica, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:462, 1928.

chronic tonsillitis, neoplasms, nephropathy, endocarditis, cryptogenic fevers and chronic rheumatism following angina. He argued that, whatever their function, it must fulfil its purpose in early youth and decrease with advancing age, and that the immediate and later dangers of the causes leading to tonsillectomy counterbalance the hypothetic damage done by the cessation of the function of the tonsils. Schneyer,[46] of Vienna, recommended tonsillectomy for acute rheumatism, polyarthritis and secondary chronic polyarthritis as a result of the first named disease. In the primary chronic arthritides there seems to be no causal nexus with infection of the tonsils, while in definite neuralgias and myalgias, tonsillectomy occasionally is of benefit.

Coombs,[47] of Bristol, England, considered that the finding of germs in the pericardial sac, subcutaneous nodules, cerebrospinal fluid, etc., is sufficient evidence of the fact that rheumatism is associated with an actual bacteremia. He thought the evidence for and against tonsillectomy hard to appraise; he operated only when there was an associated adenitis, or when removal of the tonsils was indicated because of their size, even apart from the coexistence of rheumatic infections. More than once he saw a severe recrudescence of the infection follow the excision of tonsils that had recently been the seat of an acute inflammation. Miller,[48] reporting in 1926 for a Subcommittee of the Science Committee of the British Medical Association on Rheumatic Heart Disease in Children, said: "The effect of tonsillectomy on the rheumatic infections of childhood has, up to the present, been mainly investigated by a follow up method. The results thus obtained have, as yet, proved very contradictory, and no judgment on the effect of the operations can be formed on them." He suggested as a "method of investigation which is far more applicable to the problem, the close study of the rheumatic infection as it occurs in children whose tonsils have been completely removed." Pemberton[49] studied 400 cases in soldiers. He considered the removal of foci of infection not always successful in relieving arthritis and not always the prime indication. When considered a contributing factor and remembered as that only, and not as a cure in itself, the operation is justifiable. Poynton[50] in the 1928

46. Schneyer, J.: Zur Frage der Indikationsstellung zur Tonsillektomie bei Gelenk und sogenannten rheumatischen Erkrankungen, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **13**:592, 1928-1929.

47. Coombs, C. F.: The Diagnosis and Treatment of Rheumatic Heart Disease in Its Early Stages, Brit. M. J. **1**:227 (Feb. 8) 1930.

48. Miller, R.: Report on the Effect of Tonsillectomy on Rheumatic Infection in Children, Brit. M. J. **2**:16 (July 3) 1926.

49. Pemberton, R.: The Nature of the Influence of Focal Infection and the Means Necessary to Meet It, Tr. Am. Laryng. A. **33**:142, 1923.

50. Poynton, F. J.: Rheumatic Heart Disease in Childhood, Tr. M. Soc. London, 1928, p. 313.

Lettsomian Lectures before the Medical Society of London, stated that he thought that there should be some collective studies of cases of rheumatism in children without tonsils. "If this proves to be frequent it must influence our procedure and make us tend to be cautious. Personally, I do not think that there is any more practical problem in the prophylactic treatment of rheumatic heart disease that requires more immediate attention, than does the correct line to take with the tonsils; for routine operation requires complete justification." Collins [1] said: "The incidence of certain non-respiratory diseases varies with the condition of the tonsil. The incidence of illness from rheumatism, heart conditions, cervical adenitis, and ear conditions tends to be lowest among children with normal tonsils, higher among those with defective tonsils, and highest of all among those with removed tonsils. Presumably, these more or less chronic conditions clear up only slowly, if ever, after the tonsils have been removed. For this type of condition, special treatment in addition to the removal of tonsils may be necessary." Hajek [51] felt that up to 1925 there had been no satisfactory statistics on the effects of tonsillectomy, and that results from diagnosis by elimination are unreliable. He pointed out the fact that physicians are of two opinions: 1. As far as diseases following tonsillitis—rheumatism, endocarditis, etc.—are concerned, the tonsils should not be considered as the primary site of the infection; their infection is simply a simultaneous manifestation of a septic infection at some other site. If one accepts this view, there is no justification for the removal of the tonsils, as the infection does not proceed from there. 2. The tonsils are primarily at fault, since numerous autopsies have shown the great probability that the tonsils are the primary entrance gates of infection, and microscopic examinations have shown severe injury to the tonsillar tissue. Furthermore, experience proves that it is often possible to ameliorate or inhibit long-standing rheumatic infections by tonsillectomy.

Mygind [52] connected tonsillitis with rheumatism, since patients as a rule suffer from a latent chronic angina long before a rheumatic fever develops. He stated that tonsils are not always necessary to rheumatic fever, since patients without tonsils may contract the disease. Lindberg,[53] of Sweden, spoke from the point of view of a children's physician when he said that tonsillectomy rarely seems to benefit children. It is not indicated in rheumatic infections, should not be undertaken from a prophylactic standpoint and does not prevent relapses. Hajek,[51]

51. Hajek, M.: Die Tonsillektomie, Wien. med. Wchnschr. **74**:17, 1924.

52. Mygind, S. H.: Quelques observations sur les rapports entre la tonsillite et les infections dites rhumatismales aiguës et la néphrite hémorragique aiguë, Acta oto-laryng. **6**:335, 1924.

53. Lindberg, Gustaf: Ueber Eingriffe an den Tonsillen vom Standpunkt des Kinderarztes, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **11**:752, 1927-1928.

of Vienna, thought the success of tonsillectomy for relative indications, in which he included rheumatism, endocarditis and nephritis, always doubtful. Hutter,[54] of Vienna, thought that it would by all means be a mistake to recommend tonsillectomy in all cases of rheumatism, because the question of whether acute or chronic recidivous polyarthritis is or is not always due to the tonsils needs a great deal of further study. Schoen,[55] of Germany, followed 100 cases in which tonsils were removed for diseases of the joints, endocarditis or nephritis, and found a cure of acute rheumatism seldom accomplished. He thought that the operation had some effect in preventing relapses. Jarlov and Kragh,[56] of Denmark, discussed 89 cases of rheumatic infection and concluded: "Tonsillectomy cannot be credited with any appreciable influence on the cure or amelioration of rheumatic diseases of the joints."

Campbell and Warner[57] contrasted groups of children at Guy's Hospital, 843 with, and 124 without tonsils, and found 15.3 per cent of the former and 15.6 per cent of the latter to have rheumatism. They said that many enthusiasts claim that tonsillectomy would have prevented the first manifestations of rheumatism, but that their statistics do not support this view. They found no evidence that the tonsils of rheumatic children are more septic than those of nonrheumatic children attending the outpatient clinic. The frequency of tonsillitis, the septic appearance of the tonsils and the degree of enlargement of the lymph glands are similar in the two groups. Moreover, complete enucleation of the tonsils before there were any signs or symptoms of rheumatism (on an average, two years before) did not prevent its onset, diminish its frequency or in any way lessen the incidence of rheumatic carditis. Thus there is no evidence to support the theory that tonsillectomy should be performed as a routine measure at an early age to prevent rheumatism.

Boas and Schwartz[58] said: "In spite of our increasing knowledge of rheumatic fever, there is a persistent tendency to focus attention too exclusively on the heart and too little on the systemic infection. It is true that the enthusiasm for the eradication of foci of infection in the tonsils and teeth has led toward a broader concept of the nature of

54. Hutter, Fritz: Tonsillen und interne Erkrankungen, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:88, 1928.

55. Schoen, R.: Erfahrungen über den Wert der Tonsillektomie bei internen Krankheiten, Klin. Wchnschr. **7**:2268, 1928.

56. Jarlov, E., and Kragh, J.: Die Bedeutung der Tonsillektomie bei chronischen Gelenkerkrankungen, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:711, 1928.

57. Campbell, M., and Warner, E. C.: Rheumatic Disease in Children, Lancet **1**:61 (Jan. 11) 1930.

58. Boas, E. P., and Schwartz, S. P.: Some Modes of Infection in Rheumatic Fever, Am. Heart J. **2**:375, 1927.

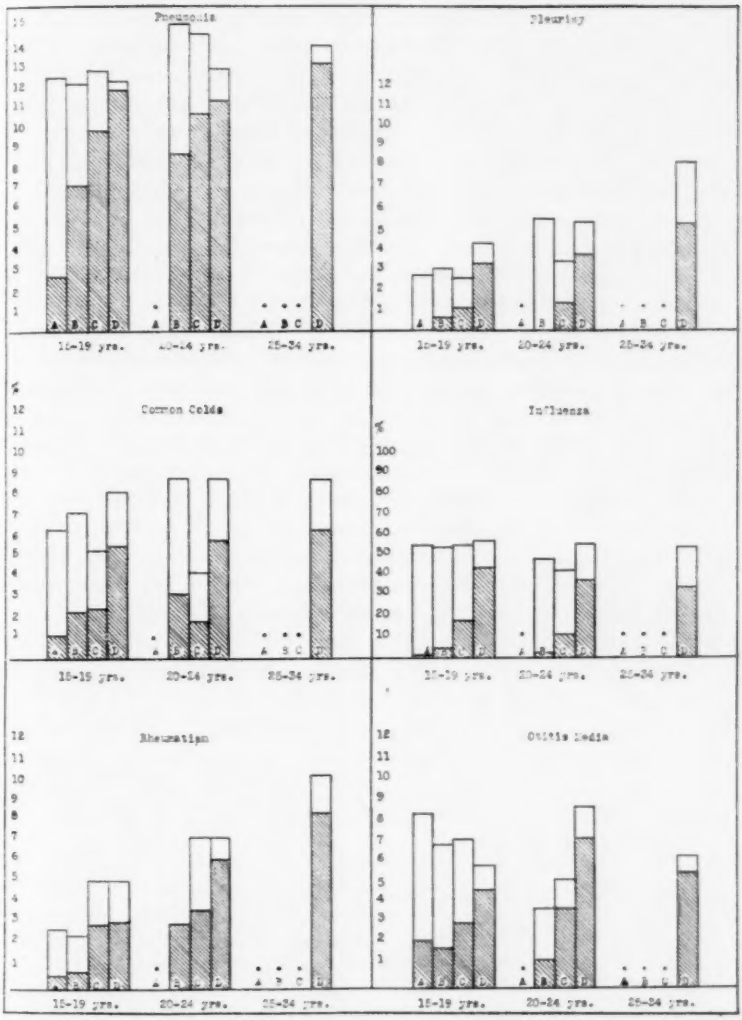

Chart 6.—Incidence of infections of the respiratory tract, according to age and the year when the tonsils were removed.

rheumatic heart disease, but the results of these measures have been rather sterile in their benefit to the patients and to the progress of knowledge. . . . Of what avail is tonsillectomy when the virus may persist in the heart, synovia, or subcutaneous nodule for months at a time, ready to give rise to infection?"

The history of rheumatism in the present study is inaccurate and probably includes many kinds of painful experiences: toxic, infectious, metabolic and traumatic arthritides and myositides, as well as cases of acute articular rheumatism. The groups of persons with normal and pathologic tonsils had about equal experience with this type of pain, whereas those whose tonsils had been removed showed about twice the percentage of incidence (table 2 and chart 2). The percentage difference is not statistically significant between the groups of those with normal tonsils and those with pathologic tonsils, but is significant between the groups of those with normal tonsils and those with tonsils that have been removed (tables 3 and 4). Of all systemic infections rheumatism probably offers the chief indication for the removal of tonsils. It was found in the present study that a high proportion of persons whose tonsils had been removed had "rheumatism" before operation (tables 5, 6 and 7 and chart 6). Both in the 15 to 19 and in the 20 to 24 year groups, those whose tonsils were removed before 10 years of age suffered less than those whose tonsils were removed in later years. However, in the group from 15 to 19 years of age those whose tonsils were removed before 10 years of age had considerable "rheumatism" following tonsillectomy.

From the cases studied, the arguments as to the value of removing the tonsils as a prophylaxis for "rheumatism" do not seem conclusive. If tonsillectomy is of value here, its influence seems of minor, rather than of major importance. The literature on the subject is extensive and varied in its arguments. In recent years there seems to be an increasing tendency to question the preventive or curative value of tonsillectomy for rheumatism.

RELATION TO CHOREA

Chorea has frequently been included in the group with tonsillitis, rheumatism and carditis, in which tonsillectomy was recommended as a prophylaxis and cure. Kaiser[11] found that chorea occurred only slightly less often following tonsillectomy: in 0.4 per cent of 1,200 children without tonsils as compared with 0.5 per cent of the same number of children with tonsils. The incidence of carditis following chorea, however, was decidedly less in the tonsillectomized children. Cummings[32] listed chorea as an indication for removal of the tonsils. Farnum[59]

59. Farnum, W. B.: Tonsillectomy: The Effect on Existing Cardiac Disease in Adults, Am. J. M. Sc. **176**:474, 1928.

studied 526 patients in a cardiac clinic before and after tonsillectomy, 5.1 per cent of whom had had chorea. He stated that in this group tonsillectomy did not seem to have a great effect on the recurrence of chorea, as about 20 per cent of cases recurred in both the tonsillectomized and the nontonsillectomized group. Crowe, Watkins and Rothholz [6] did not find tonsillectomy satisfactory in curing patients who had chorea. In discussing Pratt's [60] paper, "The Results of Tonsil Operation," McCullock said: "We have come to look at the tonsils as a focus of infection causing rheumatic fever, heart disease and chorea." Barlow, in continuing the discussion, pointed out "the tendency on the part of the physician to imply brilliant results where there is no ground for such an attitude." Findlay, Macfarlane and Stevenson [39] concluded that a preliminary tonsillectomy may render a person less susceptible to rheumatic arthritis, but not to chorea.

Although there was a history of much less chorea than of rheumatism among the young women entering the University, the relationship of the frequency of chorea in the three groups—those with normal, those with absent, and those with pathologic tonsils—was much the same as that of rheumatism (table 2 and chart 2). Those whose tonsils had been removed had about twice the percentage of chorea shown by those in the other two groups. Those with pathologic tonsils had had slightly more chorea than those with normal tonsils, which is not the case with rheumatism. Statistical value can be credited to differences in the percentage incidence of chorea in the group with normal tonsils and in the group of those whose tonsils have been removed, but not between the groups with normal tonsils and those with pathologic tonsils (tables 3 and 4).

RELATION TO DISEASES OF THE HEART

The increasing frequency of disease of the heart as a cause of death has focused attention on the etiology of cardiac pathology and on the methods of preventing damage to the heart.

Kaiser,[61] from 1919 to 1921, surveyed 48,000 school children in Rochester, N. Y., and found rheumatic heart diseases in 450, or 22.2 per cent of the 20,000 who had had their tonsils removed, and in 817 or 2.9 per cent of the 28,000 who were not operated on. In many of the children in the former group heart disease developed before enucleation of the tonsils, since a careful analysis of 478 cases of carditis showed that the condition developed in 83 per cent before removal of the

60. Pratt, F. J.: Results of Tonsil Operation: Questionnaire Report, Arch. Otolaryng. **4**:142 (Aug.) 1926.

61. Kaiser, A. D.: Relation of Tonsils to Acute Rheumatism, Am. J. Dis. Child. **37**:559 (March) 1929.

tonsils and in 17 per cent following tonsillectomy. Nobel and Hecht,[62] reporting from the University Clinic in Vienna, stated that a relation between diseases of the tonsils and other organic diseases, such as rheumatism, endocarditis and nephritis, frequently exists, but that as a rule it cannot be diagnosed by an examination of the tonsil alone. A seminar of Viennese physicians,[63] meeting in 1928 to discuss the indications for removal of the tonsils, especially for general diseases, expressed the belief that the exacerbations of endocarditis and nephritis that frequently follow tonsillectomy speak for the tonsillogenic cause of the disease; they thought that, if possible, removal of the tonsils should not be undertaken until after the acute stage of the disease. Haardt [64] agreed with the Viennese group as to the time for removing tonsils, since in twenty-one patients operated on at an early stage, two showed symptoms of marked general infection, with elevation of temperature to 40 C. (104 F.). Schoen [55] found tonsillectomy important in inhibiting relapses of endocarditis. Farnum [59] studied 526 patients in a cardiac clinic. He stated that in adults with existing cardiac disease, the hope for improvement from tonsillectomy has been based on a shaky foundation. If tonsillectomy is to be generally used as a definite therapeutic measure in cardiac disease, its best results will be obtained before the incidence of cardiac infection or very early in its course. Rheumatic carditis in all its manifestations is but one phase of a generalized infection spoken of as rheumatic fever. Removal of the tonsils, although accomplished before carditis occurs, will not prevent its occurrence. The removal of the tonsils alone will not guarantee a halt in the progress of existing cardiac disease because the cause of the infection may still be present in the throat or elsewhere in the body. The preventive treatment should be based on raising the individual resistance to infection by all possible means.

In the histories and physical observations in this study, considerable attention was given to cardiac conditions, since placement in physical education classes in the university depends on the entrance examination. Evidence of damage to the mitral valve was less among those with normal tonsils than among those with absent or pathologic tonsils (table 11 and chart 7). The latter two groups seem to suffer equally. It may be that in a high percentage of cases hearts are permanently damaged by pathologic tonsils before tonsillectomy, or persons susceptible to

62. Nobel, E., and Hecht, A. F.: Ueber die Tonsillenfrage, Klin. Wchnschr. **4**:1049 (May 28) 1925.

63. Seminar of Viennese Physicians: Wann sollen die Tonsillen entfernt werden und besonders bei welchen internen Krankheiten? Wien. klin. Wchnschr. **41**: 867, 1928.

64. Haardt, W.: Zur Frage des Zeitpunktes der Tonsillektomie beim Peritonsillarabscess, Zentralbl. f. Hals-, Nasen- u. Ohrenh. **12**:20, 1928.

tonsillar disease are also susceptible to cardiac damage. The same agent that causes damage to tonsillar tissue may, without the relationship of cause and effect, cause damage to the heart. Lesions to the aortic valve, although few, seemed to indicate a protective effect of tonsillectomy, since the group whose tonsils had been removed showed

TABLE 11.—*Condition of the Heart as Related to That of the Tonsils*

	Tonsils											
	Normal		Absent		Pathologic		Remnants		Buried or Projecting		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Mitral damage	84	2.05	140	3.45	95	3.42	7	2.17	23	2.28	349	2.85
Aortic damage	22	0.54	10	0.25	23	0.83	1	0.31	5	0.50	61	0.50
History of cardiac disease	132	3.23	207	5.10	84	3.02	8	2.48	45	4.46	476	3.88
Total number in group	4,091		4,058		2,779		322		1,010		12,261	

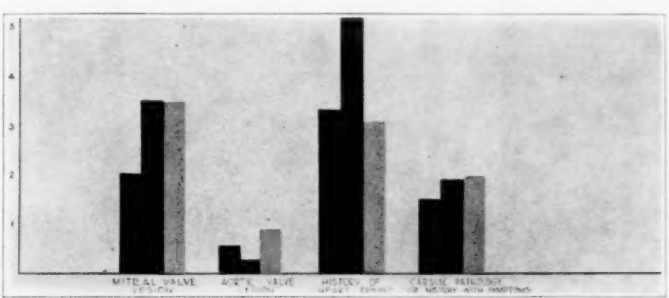

Chart 7.—Incidence of diseases of the heart. In this and chart 8 the black column indicates the group with normal tonsils, the next column those whose tonsils had been removed and the third column those with pathologic tonsils. Scale indicates per cent.

about one-half of the percentage of damage, as did those with tonsils judged as normal, and about one third the percentage of damage of those with pathologic tonsils. If all observations relative to the tonsils and cardiac conditions were of this pattern, the evidence in favor of tonsillectomy as a prophylaxis against cardiac disease would be clear. Although the diagrams and tables look convincing, no differences in percentages between the condition of the aortic valve in tonsil groups have statistical weight, and such differences as do occur must be taken as suggestive and not as final (tables 3 and 4). The history of cardiac disease, with or without accompanying physical observations, was approximately equal for the group with normal tonsils and that with pathologic tonsils, but considerably greater for the group with absent tonsils. Since the combined damage to the mitral and aortic valves in

the group with pathologic tonsils is not as much greater than that in the group with absent tonsils, as is the history of heart trouble in the group with absent tonsils greater than a similar history in the group with pathologic tonsils, some slight hint is offered of the curative action of tonsillectomy in early cardiac involvement.

The same lack of conviction as to the relationship between the condition of the tonsils and rheumatism is found in both the literature and the results of the present study for the relationship between the tonsils and cardiac conditions. Here, also, recent investigators tend to question the previously accepted relationship of cause and effect.

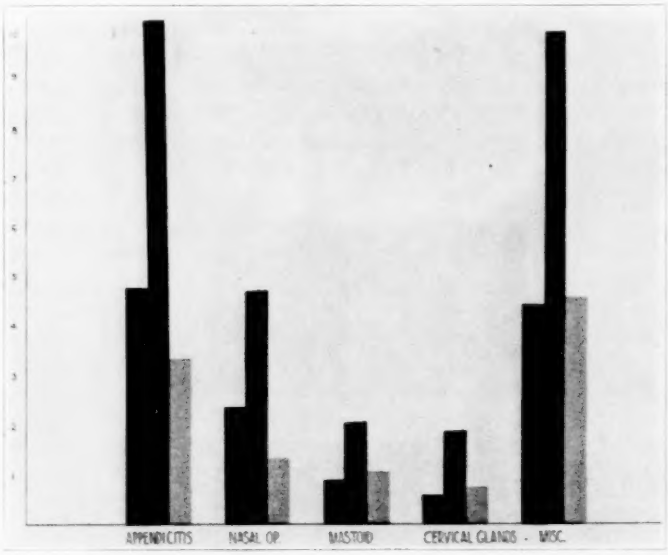

Chart 8.—Incidence of operations, by groups. Scale indicates per cent.

HISTORY OF OPERATIONS

Only the operations resulting from infectious processes and structural defects are considered (table 12 and chart 8). Those necessitated by mechanical defects, such as the plating or wiring of fractures, the removal of foreign bodies and the transplanting of tendons, are not included.

The correct interpretation of the observations on operations is probably impossible. The mental attitude toward medical care and operations in particular is apparent in that the groups accepting tonsillectomy accepted other operations in much greater numbers than did those with normal or pathologic tonsils. Even religious principle may

play a part here. It is possible that some persons with pathologic tonsils, refusing the advice to have their tonsils removed, also refused an appendectomy or delayed it too long and, through death, lessened the number of those entering the university with pathologic tonsils and with a history of appendectomy. This cannot, however, account for the entire difference between the greater number of those with normal tonsils and a history of appendicitis than those with pathologic tonsils and a similar history (table 12 and chart 8). In the group with pathologic tonsils many acute abdominal pains may have subsided undiagnosed, without operation, and their sufferers survived more by good luck than by good management. Considering the history of appendicitis without operation, it is apparent that all persons whose ton-

TABLE 12.—*The Incidence of Operation, According to the Condition of the Tonsils*

	Tonsils											
	Normal		Absent		Pathologic		Remnants		Buried or Projecting		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Appendectomy	198	4.73	419	10.14	127	4.48	24	7.29	55	5.26	823	6.57
Operation on glands of neck	24	0.57	74	1.79	28	0.99	3	0.91	9	0.86	138	1.10
Nasal operation	85	2.03	193	4.67	35	1.23	12	3.65	17	1.62	342	2.73
Mastoid operation	32	0.76	81	1.96	20	0.72	3	0.91	7	0.67	143	1.14
Total number in group	4,185		4,134		2,836		329		1,046		12,530	

sils had been removed were not operated on when a diagnosis of appendicitis was made. Over 3 per cent of those in the group with normal tonsils and of those in the group with pathologic tonsils gave a history of appendicitis without operation, whereas over 6 per cent of the group whose tonsils had been removed gave a similar history (table 2).

SUMMARY

1. The histories of young women entering the University of California during the last ten years were transferred to punch cards.

2. Of these cards, 12,530, representing white women of from 15 to 34 years of age, were sorted and tabulated as to the condition of the tonsils and as to the incidence of illnesses and operations in the three groups; the results showed: 4,185 with normal tonsils, 4,134 with absent tonsils and 2,836 with pathologic tonsils.

3. The inaccuracies of the histories, observations and method were considered.

4. Tables and diagrams of the incidence of disease and operation, with standard errors of differences in percentages in the groups are presented.

5. The cards were sorted according to age groups, from 15 to 19, from 20 to 24 and from 25 to 34 years, and according to the condition of the tonsils for the history of disease and of operation.

6. The cards of the group with absent tonsils were sorted, by age groups, to indicate whether the disease or operation preceded or followed the tonsillectomy.

7. The cards of those without tonsils were sorted according to (1) age groups; (2) the age when the tonsils were removed, from 0 to 4, from 5 to 9, from 10 to 14, and 15 years and over, and (3) for facts in the history.

8. Tables and diagrams present the observations made in this study.

9. Facts not discussed in the text are included in the diagrams and tables in the hope that they may serve as source material.

10. The literature concerning the relation of the condition of the tonsils to the incidence of measles, mumps, chickenpox, whooping cough, scarlet fever, diphtheria, infections of the upper respiratory tract (influenza not included), tonsillitis, otitis media, rheumatism, chorea and cardiac conditions has been partially reviewed.

CONCLUSIONS

1. One third of 12,530 young white women who entered the University of California between 1920 and 1929 had had an operation for the removal of tonsils; one-third were thought to have normal tonsils, and the remaining one-third had pathologic tonsils, remnants of tonsils or buried or projecting tonsils to which no further designation was given.

2. The group with normal tonsils and the group with pathologic tonsils differ by small percentages, which are statistically insignificant in the incidence of the following diseases and operations reported in the histories: measles, mumps, chickenpox, whooping cough, scarlet fever, diphtheria, pneumonia, pleurisy, chronic colds, rheumatism, chorea, operations for appendicitis, mastoiditis, cervical glands and operations on the nose.

3. The group with absent tonsils gave a history of higher incidence of all illnesses and operations than did either the group with normal tonsils or the group with pathologic tonsils. The fact that children who are often ill are the ones most frequently operated on is offered as a possible explanation for this higher incidence of illness.

4. The proportion of the amount of illness reported before and after tonsillectomy suggests that the removal of tonsils had little influence in lessening the susceptibility to most infections. The lack of proper comparative data lessens the value of this conclusion.

5. The age when the tonsils were removed had no influence on the total incidence of measles, mumps, chickenpox, whooping cough, pneumonia and influenza, but early removal seemed to have a slightly favorable influence on the incidence of scarlet fever and, to a less extent, on that of diphtheria. The effect of the age of removal on chronic colds, rheumatism and otitis media was not conclusive.

6. A review of the literature relative to the effect of the condition of the tonsils on general health reveals a great lack of accurate information on the effect of tonsillectomy, when one considers the number of operations that have been performed. Opinions as to the indications for, and the value of, tonsillectomy vary widely. There is a growing tendency to question the value of tonsillectomy as a prophylaxis against infectious diseases and as a preventive measure or cure for such systemic diseases as rheumatism, chorea and carditis.

CHRONIC ENDEMIC ERGOTISM

ITS RELATION TO THE VASOMOTOR AND TROPHIC DISEASES *

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Epidemic ergotism has practically been extinct since the end of the last century. The more careful cleaning of the rye seed before planting and milling undoubtedly accounts for the great reduction of the torturing pains and mutilations that resulted from the eating of rye bread infected with ergot. Our economic system, through which grains are stored for long periods, is another important element in preventing ergotism. It is well known that the toxicity of ergot decreases with age. During the epidemics it was noticed that ergot was most harmful soon after the harvest, that the toxicity decreased considerably toward spring, and that by summer the ergot was practically harmless.

If it were not for the careful cleaning and long storing of the grain, conditions similar to those that occurred during the epidemics might be witnessed, as even today many rye fields are heavily infected with ergot. Atanasoff [1] said:

> Grains, especially rye, in some seasons and in some fields are infected so heavily that every head may have one or more sclerotia, as was reported from Wisconsin in 1917.
>
> Cases where 20 to 50 per cent of the heads were infected with ergot have been reported from various parts of the United States and Europe.
>
> The amount of ergot for 1917 in Connecticut ranged from one to five per cent. Decrease of the yield (of rye) by as high as 20 per cent has been reported from Russia (as a result of ergot infection).

Ergot has been found in every continent on the globe. It attacks all the grains and grasses, but rye is its principal host. In North America it has been found in Vermont, Connecticut, New York, Michigan, Tennessee, Indiana, Wisconsin, Minnesota, Iowa, Kansas, Wyoming, Montana and other states besides various localities in Canada.

The importance of the present day infection can be judged by the defensive measures of the farmers and millers to remove the fungus. Many methods, such as sifting, screening and sedimentation, are employed, which Atanasoff said may reduce the amount of ergot to from 0.06 to 0.17 per cent. It is, of course, not expected that such

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* From the Pathological Department of the Sydenham Hospital.

1. Atanasoff, D.: Ergot of Grains and Grasses, Monograph, U. S. Dept. Agric., Washington, 1920.

a reduction could occur where the infection with ergot was very heavy. I have examined many samples of rye flour from various regions, and have found few that were not contaminated with ergot; some of them contained a considerable quantity.

A study of the literature of epidemic ergotism and my experimental investigations of ergotism in fowl have suggested to me the possibility that the cause of some of the vasomotor and trophic diseases can be traced to endemic ergotism. Of course, it would be impossible to prove this until more facts have been obtained. However, I believe that there is sufficient evidence in the form of pathologic analogies and the widespread consumption of ergot to make this fungus the subject of greater study in relation to such diseases as thrombo-angiitis obliterans, Raynaud's disease, erythromelalgia, acro-asphyxia, scleroderma, sclerodactylia, multiple neurotic gangrene, dermatomyositis and other such diseases of unknown origin. The relationship between ergotism and this group of diseases was hinted at in an article in which I attempted to show the similarity of thrombo-angiitis obliterans and ergotism (gangrenous form). Much of the details in the etiology, pathology, toxicology and symptomatology of these two conditions, which are omitted here, will be found in that article.[2]

Considering the amount of rye infected with ergot that is consumed here and abroad, it is surprising that cases of endemic ergotism are so rarely reported.[3] It may well be that chronic endemic ergotism occurs in the guise of the vascular, vasomotor and trophic diseases mentioned. These sequelae to ergot poisoning are perhaps overlooked because of the mildness of the original intoxication and the insidious onset of the later manifestations.

That Raynaud [4] suspected ergot to be the cause of the disease named after him is borne out by his experimental attempts to produce this

2. Kaunitz, Julius: The Pathological Similarity of Thrombo-Angiitis Obliterans and Endemic Ergotism, Am. J. Path. **6**:299-315 (May) 1930.

3. Since writing this, I have come across the article of Robertson and Ashby (Ergot Poisoning Among Rye Bread Consumers, Brit. M. J. **1**:302, 1928) and Morgan (Report on an Outbreak of Alleged Ergot Poisoning by Rye Bread in Manchester, J. Hyg. **24**:51, 1929) of a small outbreak of acute ergotism occurring in Manchester as late as 1928. It affected only the members of the Jewish population who ate rye bread. The rye flour contained approximately 1 per cent ergot, which appeared to be harmful only soon after the harvest, when it was fresh. The vasomotor and trophic symptoms were milder than those mentioned of the epidemics. Improvement was observed in some cases when the use of rye bread was discontinued.

4. Raynaud, Maurice: On Local Asphyxia and Symmetrical Gangrene of the Extremities, Trans. by Thomas Barlow, Selected Monographs, London, New Sydenham Society, 1888, p. 130.

disease in animals. Ehlers[5] not only suspected Raynaud's disease but also erythromelalgia, acrodynia and other vasomotor disturbances as being due to ergot.

SUSCEPTIBILITY

General Considerations.—The Abbé Tessier[6] formed a good judgment of the conditions likely to promote an outbreak of ergotism (he speaks of La Sologne):

> . . . these are three: 1. That the district was damp and foggy; 2. that the vegetable products were ill-thriven and stunted; 3. that the inhabitants were in bad health, being reduced by want and malaria.

It was noticed that those persons whose diet also contained milk, cheese or meat in addition to rye bread suffered less severely or not at all. The rôle played by a diet almost exclusively of rye bread or the addition to it of dairy foods and meats deserves consideration. These animal foods may serve as a protection against ergotism in the same way as they do against pellagra, another grain disease.

The increased susceptibility brought about by starvation, misery and ill health mentioned by Tessier is true of many other diseases.

Sex and Age.—In a survey of sixty-eight epidemics, Krysinsky[7] found that with one exception the gangrenous form of ergotism affected the males exclusively. The convulsive form affected the women, children and the aged. Tessier[8] observed that the spurred rye acts with less force on females. Renauldin[9] stated that the gangrenous form of ergotism does not affect females. Noel,[10] surgeon of the Hotel Dieu of Orleans, describing an epidemic of 1710, said of ergot: ". . . attacks men by preference . . . what is most astonishing, does not attack women." What is true of epidemic is also true of medicinal ergotism. In spite of the tremendous quantity of ergot administered to women in this country—from 170,000 to 264,000 pounds

5. Ehlers, Edvard: Ignis sacer et Sancti Antonii, Kjøbenhavn, Ernst Bojesen, 1895, pp. 68-79.

6. Tessier, Abbé: Recherches sur le feu Saint Antoine, par Jussieu, Raulet, Sailant, Tessier, etc., Hist. Acad. roy. d. sc., 1776; quoted from Allbutt and Rolleston: System of Medicine, New York, The Macmillan Company, 1906, vol. 2, part 1, p. 886.

7. Krysinsky, Stanislaus: Pathologische und kritische Beiträge zur Mutterkornfrage, Monograph, Jena, Gustav Fischer, 1888.

8. Tessier, Abbé: Traite des maladies des graines, Paris, 1783, 8 vols.; quoted by Neale, Adam: Spur or Ergot of Rye, London, H. Phillips, 1828, vol. 8, p. 18.

9. Renauldin: Dictionaire des sciences médicales, ergotisme, Paris, 1815, vol. 8; quoted by Neale, Adam: Spur or Ergot of Rye, London, H. Phillips, 1828, vol. 8, p. 18.

10. Noel, quoted from Raynaud (footnote 4, p. 131).

(77,100 to 119,700 Kg.) imported yearly [11]—one rarely hears of a case of gangrene in women from this source.

When the rye is heavily infected with ergot, as during epidemics, because of the overwhelming quantity few persons escape its mutilating effects. However, when the infection is slight, only those persons who are most susceptible suffer from its effects, the intoxication being more selective and, on account of the different individual idiosyncrasies, assuming different forms of vascular, vasomotor or trophic manifestations.

One of the severest vascular conditions in this study is found in thrombo-angiitis obliterans. This disease occurs most frequently in young and middle-aged men, but is rare in women. Raynaud's disease, however, occurs more frequently in women. Ergotism, as we have mentioned, also produces gangrene in young and middle-aged males, but rarely in females. It is pertinent to consider here the possibility that men who are most susceptible to ergot are more frequently affected with the severer pathologic condition of thrombo-angiitis, while the women, who are less susceptible, are more frequently affected with a milder condition of Raynaud's disease.

SYMPTOMATOLOGY

The different symptoms and signs that occur in Raynaud's disease, such as erythromelalgia, sclerodactylia, scleroderma, etc., are well known. It is because of the distinctions in these symptoms and signs that the classification is made. It frequently happens, however, that the symptoms of two or more of these conditions are found associated. Raynaud's disease, for instance, may exhibit symptoms of erythromelalgia, sclerodactylia or scleroderma. Scleroderma frequently is found associated with sclerodactylia. It is not unusual to find symptoms and signs of the vasomotor and trophic group of diseases, especially Raynaud's disease, erythromelalgia, scleroderma, sclerodactylia, etc., associated with thrombo-angiitis obliterans. The frequent association of these various syndromes must be considered as something more than a coincidence.

In epidemic ergotism, all of the vasomotor disturbances were noted. Pallor, rubor and cyanosis were frequently accompanied by excruciating pains of a burning or cramping nature. Paresthesias, such as formication, heat, coldness and anesthesia were some of the other sensory disturbances noted. Trophic changes, such as ulceration, desquamation, shriveling or withering of the tissues or whole extremities were some of the sequelae. The pulse was found to tighten from day to day and

11. Department of Commerce of the United States, private communication.

finally to become obliterated. Cyanosis gave way to blackness, which was followed by gangrene, generally of a dry nature, in the fingers, toes, hands or feet, the entire extremity or in patches over the trunk, extremities, ears, nose or viscera. These symptoms were generally more acute than those in the group of diseases under consideration. To my knowledge, the chronic cases of ergotism that might belong to this group were not chronicled during the epidemics. They might have passed then, as they do today, for different conditions. Today, with no definite human ergotism as a basis, it is even more difficult to appraise the causal relationship of ergot. In cases of thrombo-angiitis obliterans, I was able to collect considerable evidence of the disease occurring in those who eat rye bread.

The symptoms of the vasomotor and trophic diseases that are being considered may be found in various combinations of those found in ergotism, the following of which are a few brief examples:

In thrombo-angiitis obliterans, one may find all the vasomotor disturbances manifested by pallor, rubor and cyanosis, and sensory disturbances of severe burning or cramping nature, paresthesias such as formication, coldness, heat and anesthesia. Local edema or atrophy with trophic ulcers generally occurs in the toes and fingers. These symptoms may precede or occur simultaneously with the obliteration of the pulse in an extremity. The terminal infarction usually occurs in the extremities and occasionally in the viscera, the symptoms of the latter condition resembling those of coronary, mesenteric and other visceral thromboses.

In Raynaud's disease, pallor, rubor and cyanosis may occur paroxysmally and bilaterally, in the extremities, in the tip of the nose or ears, or in patches over the body as in multiple neurotic gangrene. Local edema or atrophy with trophic ulcers and severe pain, paresthesias and anesthesias are some of the other manifestations in the affected regions. The pulse may be obliterated during the arterial spasm. Persistent cyanosis is followed by blackness and finally gangrene in the affected regions. Epileptic seizures, paroxysmal hemoglobinuria and other visceral conditions have been attributed to this condition. The distribution of Raynaud's disease is much like that of epidemic ergotism.

In erythromelalgia the vasomotor symptom is generally rubor, which is followed by cyanosis in the part of the extremity affected. Excruciating burning pains are experienced, particularly when the extremity is in the pendant position. Edema and trophic disturbances and ultimately gangrene usually follow the vasomotor phenomena. The distribution is practically limited to the hands and feet.

Chronic acro-asphyxia generally exhibits a cyanosis which, though of a chronic nature, may occasionally be paroxysmal in its attacks. Pain

is usually absent, there being instead a hypoesthesia, coldness and numbness. Edema and trophic ulcers are generally found in this condition; the distribution is practically limited to the hands and feet.

Scleroderma frequently begins with the vasomotor symptoms of Raynaud's disease. The skin is either blanched, hyperemic or cyanotic. The hard edema is followed by induration which may occur in patches or all over the body. Sensory disturbances of burning pains, formication and numbness are complained of. Trophic ulcers and gangrene, particularly the former, are commonly encountered. When sclerodactylia is an associated complication, atrophy or withering of the fingers takes place, the terminal phalanges becoming absorbed.

In dermatomyositis, as in scleroderma, the skin is said to exhibit vasomotor disturbances which are followed by edema and later induration. In some cases the muscles are markedly inflamed and excrutiatingly painful, particularly on motion. This rare disease is only mentioned because of some suggestive pathologic observations connected with it that I obtained in experimental ergotism.

ONSET AND COURSE

During the epidemics, ergotism frequently ran an acute course. Starting with shock, gastro-intestinal and nervous symptoms, death followed as after severe intoxication. In the more chronic form, the intoxication usually manifested itself immediately and occasionally many months after exposure to cold or an acute infectious disease, when gangrene of the extremities or infarcation of the viscera would ensue. During the epidemics, it was also noticed that after the amputation of one of the gangrenous limbs, the symptoms receded or disappeared until some future epidemic when gangrene of another limb became evident. The epidemics are too far removed for one to decide whether the succeeding attacks were due to the original intoxication with ergot and not to the later epidemic. There is a certain amount of evidence supporting the idea of an immunity to ergot which results from previous inoculation or ingestion of ergot. If this is true, one must consider that the secondary attacks of gangrene were not so much the result of the reingestion of ergot, but were due to the vascular lesions that the previous intoxication had caused. In horses whose hooves or tails sloughed off after intoxication with ergot, Buffum[12] noticed that gangrene was occasionally delayed two years after the original intoxication. In thrombo-angiitis obliterans, one limb after another becomes involved, until in some cases amputation has been

12. Buffum, B. C.: Grasses and Forage Plants, Wyoming Agric. Exper. Sta. Bull. **16**:223-248, 1893; quoted by Atanasoff (footnote 1).

performed on both upper and lower extremities. Occasionally, in a milder form, the same sequence has been observed in Raynaud's disease. The co-existence of endarterial lesions in apparently healthy extremities in cases of thrombo-angiitis obliterans has been demonstrated. One frequently finds many stages of this vascular disease present. It appears suggestive that as a result of earlier intoxication, vascular changes are

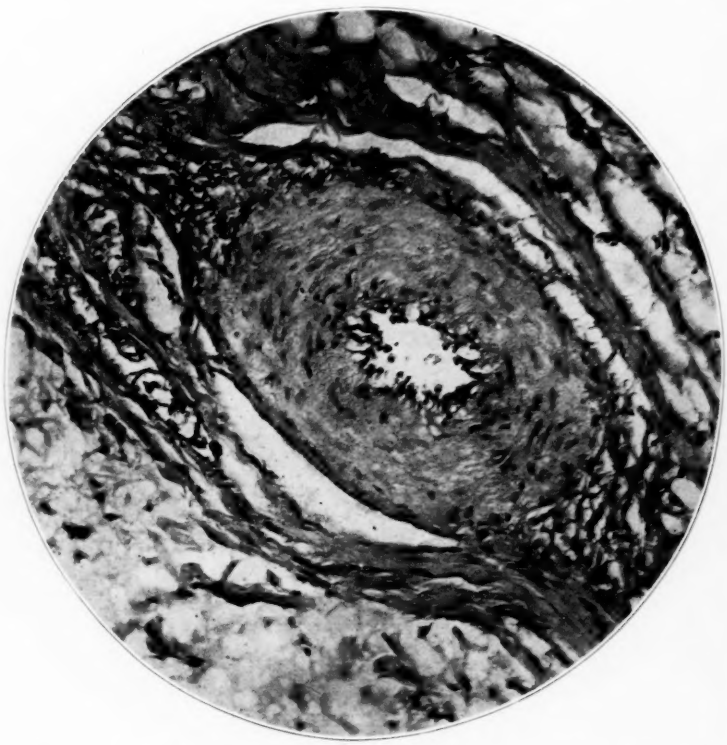

Fig. 1.—Acute ergotism. Photomicrograph of the artery of the median stalk at the base of the cock's comb. The media appears thickened and edematous. The nuclei stain poorly, suggesting attrition due to continual angiospasm. The lumen of the vessel, which is considerably narrowed, was perhaps more contracted during life. The pathologic sequelae in these vessels can only be surmised by the lesions found in figures 4 and 5, which show chronic manifestations.

provoked, particularly in the extremities. The change in the peripheral tissues results from the organic and functional interference with the circulation in these tissues. An acute onset following an acute infectious disease is frequently met with in Raynaud's disease and in erythromelal-

gia and is comparable to the manifestations of ergotism that are provoked by an acute disease long after the intoxication with ergot. In most of the diseases of this group, there is a chronic course.

PATHOLOGY

The intrinsic pathologic processes in these vascular and trophic diseases that have been considered is anything but an open book. Of

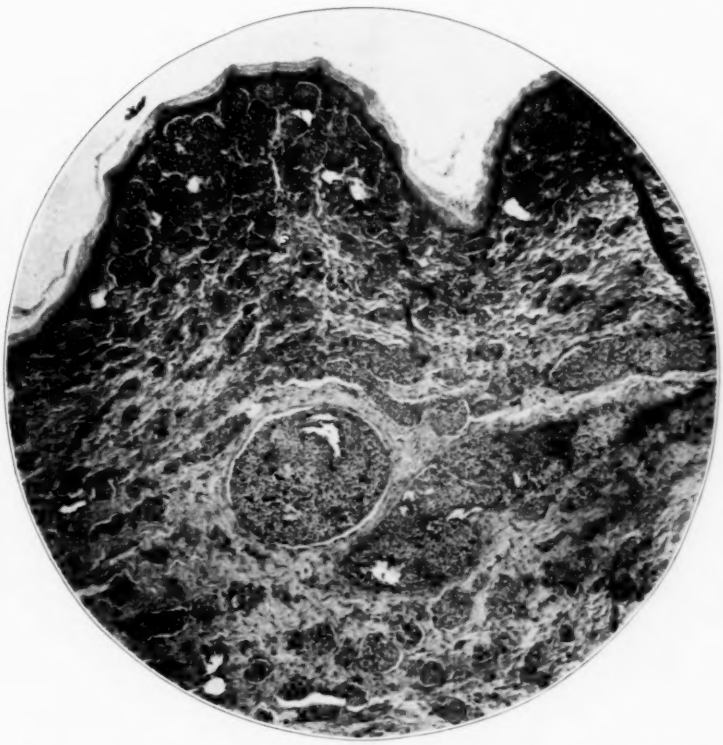

Fig. 2.—Section from the same comb as figure 1, but near to the tip of the posterior portion, proximal to a line demarcating gangrene. There is marked hyperemia throughout. The vessels are engorged, and the coats are stretched thin. The vessels contain old blood and degenerated blood pigment, evidence of the marked stasis noticed during life. The epithelial covering of the comb appears edematous. On higher magnification, the epidermal layer is slightly thickened. The marked interference with the circulation produced by the spasm of the artery (fig. 1), and the marked dilatation and stasis shown in this picture, resulted in the dry gangrene about 3 mm. distal to the place from which this section was obtained.

course, this is also true of endemic ergotism. The frequent pathologic effects, such as trophic ulcers, edema, inflamed or indurated soft tissues, gangrene, atrophy, etc., are well understood, but there is no precise knowledge of the vascular and neural changes that precede these effects.

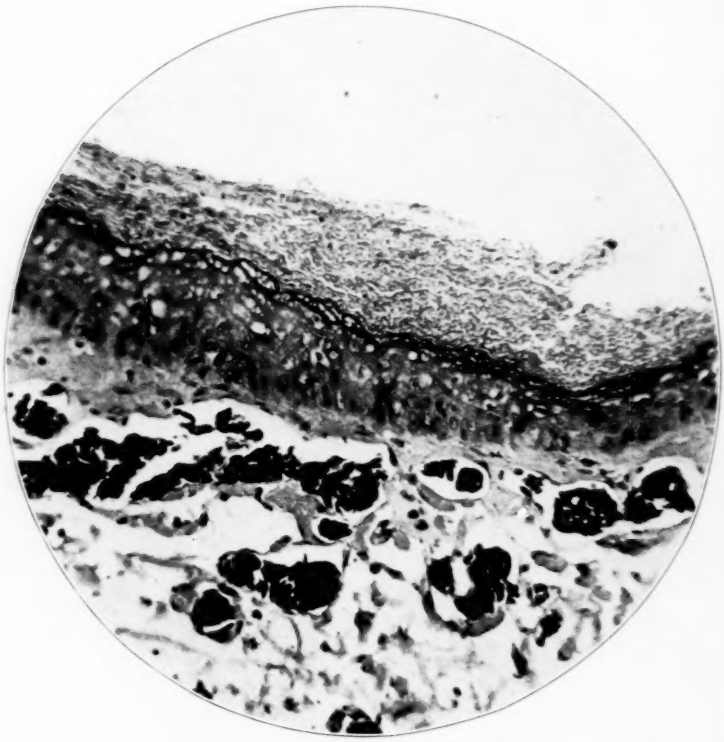

Fig. 3.—Chronic ergotism (about seven months). The section was taken from the middle of the posterior part of the cock's comb. Chronic edema, which is very evident in the dermis, is noted throughout the section. The thickened epidermis appears loosely attached. During life, this desquamated grayish scales. There were small capillary hemorrhages over the entire comb and a few ulcerations at its base. Some of the arteries appeared contracted and showed some intimal thickening. Absolute occlusion was not noticed in the vessels. The trophic changes were most probably due to the vascular dystonia. During life, the comb appeared pale at the base, slightly reddish in the middle and purplish at the tips, suggesting angiospasm at the base with dilatation and stasis at the periphery. The hard edema, scaling and vasomotor symptoms suggested the skin and subcutaneous changes described in cases of scleroderma and dermatomyositis.

Buerger,[13] who made an extensive study of this subject, particularly of thrombo-angiitis obliterans, expressed the belief that only the latter condition of this group is to be associated with any organic obliteration of the lumina of the vessel; the pathologic effects in the others arise

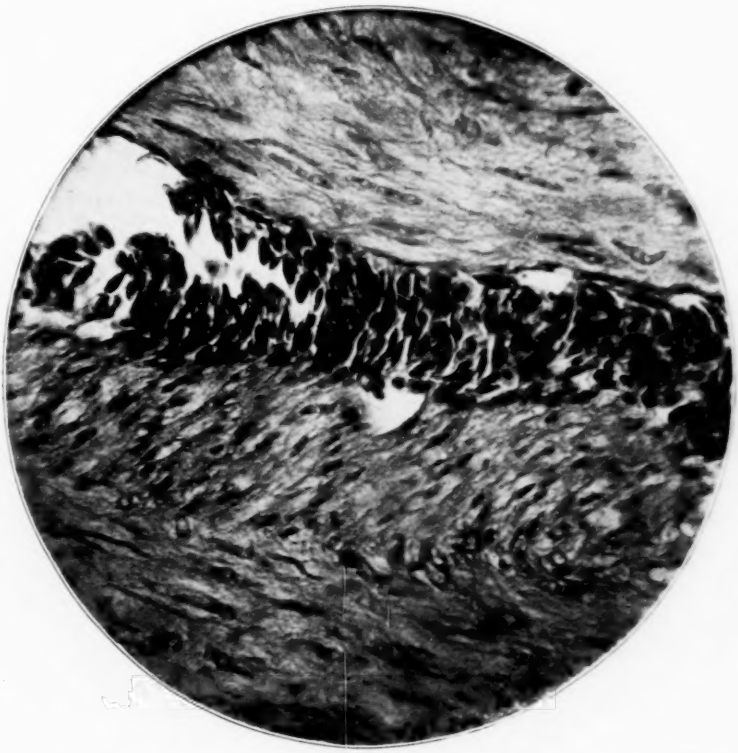

Fig. 4.—Chronic ergotism (about one year). The section was taken from the middle of the posterior portion of the cock's comb showing early hyperplasia of the intimal cells. Note the tendency of the cells to grow with their long axes radial, as in early thrombo-angiitis obliterans. The oval cells in the lumen are erythrocytes, which are nucleated in birds.

only as a result of vasomotor and neurotrophic disturbances. Although there are many who concur in this opinion, there are others who attach considerable importance to endarteritic changes, particularly in some of the smaller arteries of the extremities in Raynaud's disease and erythromelalgia. Of course, in the absence of complete organic occlusion

13. Buerger, Leo: The Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924, p. 376.

in these vessels, one must agree that additional factors are necessary to interfere with the circulation and produce trophic ulcers, chronic edema, gangrene, etc. The combination of arterial spasm and dilatation of the capillaries and venules results in a stasis, which could produce such pathologic lesions in the peripheral tissues, as I suggested. The organic changes in the vessels mentioned in the exhaustive studies of Isaac [14] and those of Cassirer and Hirschfelder [15] in patients with

Fig. 5. — Chronic ergotism, simulating thrombo-angiitis. This section was obtained about 2 mm. proximal to the one shown in figure 4. This vessel shows the later stages of thrombo-angiitis in which organization has occurred both in the intimal tissue and in an attached thrombus. The organization and fusion of both tissues makes it extremely difficult to differentiate them as separate entities.

14. Isaac, Georges Pierre: Contribution a l'étude de la pathogénie du syndrome de Raynaud (de l'importance des lésions artérielles), Thesis, Paris, L. Arnette, 1926, p. 88.

15. Cassirer, Richard D., and Hirschfelder, Robert: Vaso-motorisch-trophische Erkrankungen, Spezielle Pathologie und Therapie inneren Krankheiten, Berlin, Kraus & Brugsch, 1924, vol. 10, part 3, p. 579.

Raynaud's disease indicated that this disease is not merely a vasomotor condition. The same may be said of erythromelalgia in which endarterial and even thrombotic changes were found by Shaw [16] and others. Benoist,[17] backed by his experience and an extensive bibliography, expressed the opinion that organic changes are found in the vessels as well as degenerative changes in the cord. Although the organic changes in these two conditions do not usually compare with those of thrombo-

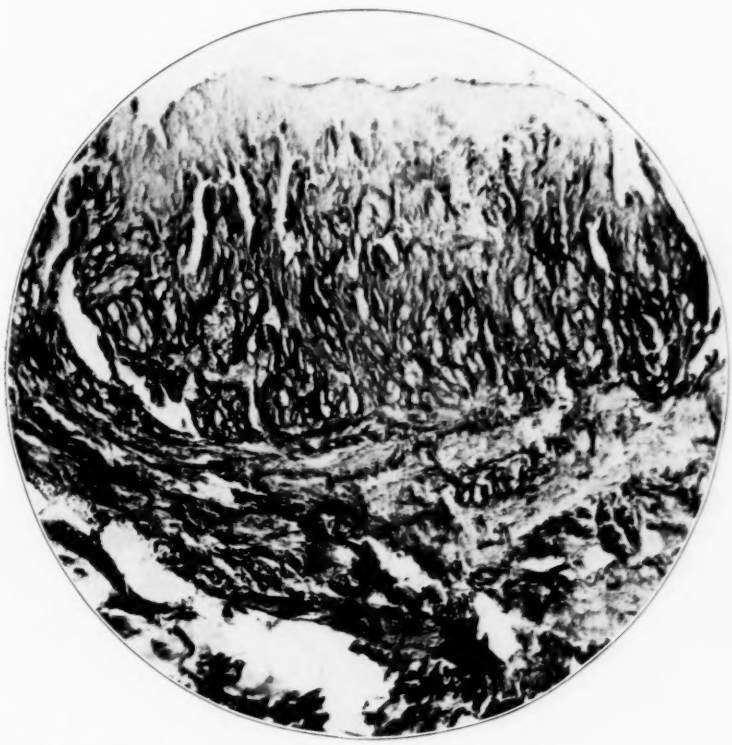

Fig. 6.—Section of a vein from a case of thrombo-angiitis obliterans. Note the arrangement of the intimal cells with their long axes radial. This is an early stage in this process, although organization has already begun.

angiitis obliterans, nevertheless they all may have a common causal relationship.

16. Shaw, H. Batty: The Morbid Anatomy of Erythromelalgia Based Upon the Examination of the Amputated Extremities of Three Cases, Brit. M. J. **1**: 662, 1903.

17. Benoist, Emmanuel: Étude sur l'érythromelalgie, Thesis, Paris, J. Rousset, 1911, pp. 169-173.

The pathologic changes in ergotism are frequently mentioned, but usually without definite description. In spite of the many epidemics, knowledge on this subject is meager. Ergotism may be distributed to any peripheral portion of the body. Gangrene has been mentioned to have occurred in every part of the extremities and trunk, the viscera

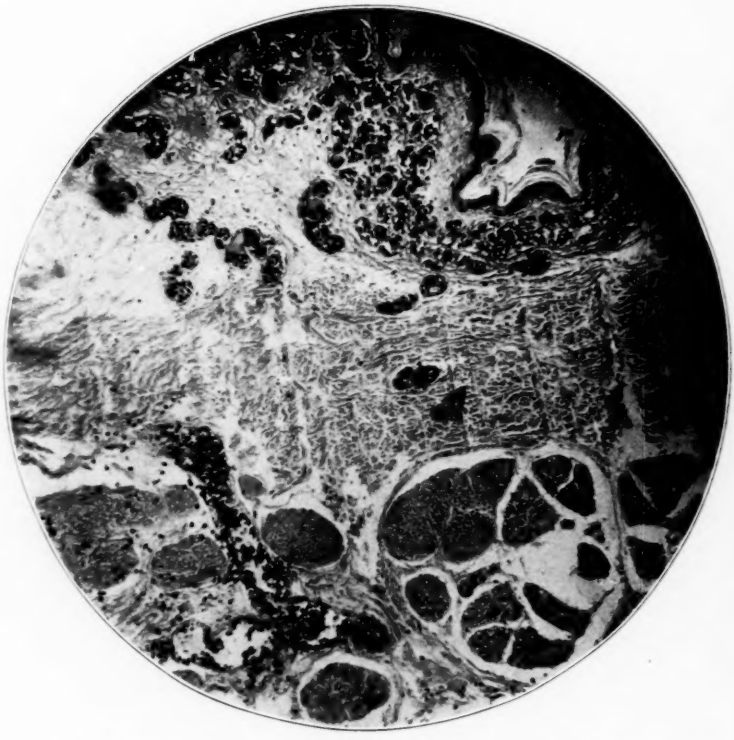

Fig. 7.—Acute ergotism. The section was taken through the skin, subcutaneous tissue and muscles of the rump of a rooster. Note the marked engorgement, particularly in the dermis. This condition appeared during life as a purpuric eruption. The marked stasis with deficient oxygenation probably accounted for this appearance. Other vessels are seen engorged in the subcutaneous tissues, some of which extend into the muscle fascicles. Many of these muscle fibers appear vacuolized in the transverse section.

and tips of the nose and ears. The report of an epidemic of acute convulsant ergotism at Viatka in 1889, written by Vinogradoff,[18] who

18. Vinogradoff, N. F.: Pathologic Anatomy of Ergotism, St. Petersburg, Vrach, 1895, pp. 585, 622 and 647.

found various types of vascular lesions in the viscera, contains perhaps the best description of these lesions. Nearly all of the large vessels contained thrombi, some of which were red, while others were composed principally of fibrin. In some of the smaller branches of the portal vein, organized thrombi were found. Some of the walls of

Fig. 8.—Acute ergotism in the same animal as in figure 7. The section was taken from the pectoral muscle, showing marked degeneration in the muscle fibers. Some fibers that appear least affected have lost the staining qualities of the normal, the striations not showing. There is marked engorgement in some of the vessels between the muscle fibers in other areas of this section. The skin that covered this area also had the purpuric appearance, as described in figure 7. Both of these lesions suggest an acute form of the more chronic disease, dermatomyositis.

the vessels were thickened with their lumina narrowed to such an extent as not to permit more than two or three erythrocytes to pass. Marked proliferation of the intimal was observed in some of the vessels, while others showed fibrosis or hyaline degeneration.

In my experimental work, I was able to produce both acute and chronic ergotism in fowls. In the acute form, the arteries (fig. 1) near the base of the comb were found contracted, and the media were swollen and hyaloid as though in a state of degeneration. On the other hand, the capillaries (fig. 2) were markedly dilated, and contained stagnant

Fig. 9.—Photomicrograph of an artery from the finger in a case of Raynaud's disease reported by Cunningham (New York State J. Med. **26**:973, 1926). The artery shows a marked proliferation of the intima, which has become organized and contains newly formed vessels, as in thrombo-angiitis. There was no evidence of actual obliteration of its lumen. One must interpret the gangrene that resulted as not being due to the organic changes in the vessels as much as to the vascular dystonia.

blood. This stagnation was probably the cause of the gangrene at the posterior tip of the comb. Evidence of stasis was also found in the skin and muscles of the pectoral and gluteal regions (fig. 7). The capillaries in both the skin and muscles are markedly dilated, the latter showing evidence of degenerative changes.

In a more chronic case, of about seven months' duration, in which many of the vessels of the comb showed endarterial hyperplasia, the comb was swollen to about double its natural width and manifested vasomotor and trophic conditions such as pallor, rubor, cyanosis (at the tips), ulcerations, fine capillary hemorrhages and desquamation of the epidermis (fig. 3). In a rooster on which autopsy was performed a year after the initial feeding with ergot, many of the vessels of the comb (fig. 4) showed endarterial hyperplasia with the intimal cells tending to grow with their long axes radial, as in thrombo-angiitis obliterans, described by Mahorner.[19] Many vessels showed organization of the thickened intimal process; one artery (fig. 5) showed an organized thrombus fused to the organized intimal process as in a later stage of thrombo-angiitis obliterans.

As no thrombus completely obliterated the lumina in the vessels of either the acute or the chronic ergotized animals, one must conclude that in these cases the destructive processes were due to the dystonic vascular conditions; that is, there was spasm in the arteries with dilatation and stasis in their terminal capillaries. I suggested that, by its interference with the nourishment of the tissues, this condition is capable of behaving as an obturating thrombus in an artery.

That ergot is capable of producing such effects is not strange when one realizes that it contains such substances as tyramine, which causes marked arterial constriction, and ergotoxine, ergotamine and histamine, which cause marked capillary dilatation.

One hesitates to attempt the unification of these vascular and trophic disturbances that have been so carefully classified as separate entities. Classification dependent on symptomatic and even pathologic differences, however, should not interfere with a unification dependent on a common cause. A difference in the lesions might depend on a difference in the ergot toxin and the idiosyncrasy of the host. Such marked differences in pathology, clinical manifestations and distribution is possible in many diseases. Such marked differences as between miliary tuberculosis and lupus vulgarus in tuberculosis make one realize the possibility that in ergotism there might be such dissimilar conditions as thrombo-angiitis obliterans and scleroderma.

19. Mahorner, H. R.: Thrombo-Angiitis Obliterans, in Brown and Allen, Mayo Clinic Monograph, Philadelphia, W. B. Saunders Company, 1928, p. 54.

Although occluding thrombi have not been obtained in our animals, one must remember that in human beings such thrombi have been described as occurring in ergotism, even in an organized state. Such observations, as well as the earlier vascular changes and the vasomotor and trophic conditions that have been demonstrated, might fit some cases of thrombo-angiitis obliterans, Raynaud's disease or erythromelalgia. It may be that on closer scrutiny scleroderma, sclerodactylia, dermatomyositis, acro-asphyxia, etc., will show organic vascular changes.

The microscopic illustrations have been described with a view of showing the possible relationship between ergotism and the vasomotor and trophic diseases under consideration. It is hoped that they will help to clarify some of the important questions in this article.

CONCLUSIONS

1. Some etiologic factors, symptoms, physical signs and pathologic manifestations have been discussed about a group of vasomotor and trophic disturbances which includes: thrombo-angiitis obliterans, Raynaud's disease, erythromelalagia, acrocyanosis, scleroderma, sclerodactylia, dermatomyositis, etc.

2. The relation of this vasomotor and trophic group of conditions to ergotism in human beings and that experimentally produced has been considered.

3. It has been shown that ergot infests our rye fields, occasionally in dangerous quantities.

4. In a study of thrombo-angiitis, it has been shown that in patients having this disease, rye bread forms a large part of the diet. A more careful study, which will correlate the diet with these vasomotor and trophic diseases, is necessary.

5. In view of our knowledge of the effects of toxic ergot, it appears advisable to employ more stringent prophylactic measures, even before there is absolute proof of my suggestion that many cases of vasomotor and trophic diseases are due to the ingestion of ergot.

MULTIPLE PULMONARY ABSCESSES SIMULATING TUBERCULOSIS

CAUSED BY THE FRIEDLÄNDER BACILLUS *

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CHICAGO

Acute pulmonary infections caused by the Friedländer bacillus group have been known since 1882 and 1883, when Friedländer [1] described the micro-organism and attributed to it the cause of pneumonia. After several years of controversy by various investigators, Fraenkel [2] in 1886 described the pneumococcus as the cause of pneumonia and assigned the Friedländer bacillus to the rôle of a secondary invader. So convincing was Fraenkel's work that many physicians accepted it without qualification. However, soon afterward, in 1886, Weichselbaum [3] showed that the bacillus of Friedländer caused 5.5 per cent of the cases in a series of more than 100 patients. It was nearly ten years before valid confirmation of this work was produced by others, although many believed in it.

Some of the most acceptable reports were given by Étienne,[4] 1895; Comba,[5] 1896; Smith,[6] 1897; Thiroloix,[7] 1897; Howard,[8] 1898; Béco,[9] 1899; Moïsejew,[10] 1900; Brinckerhoff and Thompson,[11] 1901; Kokawa,[12]

* Submitted for publication, Sept. 8, 1930.

* From the Research Laboratories of the Municipal Tuberculosis Sanitarium.

1. Friedländer: Virchows Arch. f. path. Anat. **87**:319, 1882; Fortschr. d. Med. **1**:175, 1883.
2. Fraenkel: Ztschr. f. klin. Med. **2**:437, 1886.
3. Weichselbaum: Med. Jahrb. **1**:483, 1886.
4. Étienne: Arch. de méd. expér. et d'anat. path. **7**:124, 1895.
5. Comba: Jahresb. u. d. Fortschr. d. path. Microorg. **12**:101, 1896.
6. Smith: J. Boston Soc. M. Sc. **2**:174, 1897-1898.
7. Thiroloix: Bull. et mém. Soc. anat. de Paris **11**:152, 1897.
8. Howard: Philadelphia M. J. **1**:336, 1898.
9. Béco: Rev. de méd. **19**:461, 1899.
10. Moïsejew: Bolnitschanja Gazetta Botkina **11**:889, 1900.
11. Brinckerhoff and Thompson: Rep. Boston City Hosp. **12**:149, 1901.
12. Kokawa: Deutsches Arch. f. klin. Med. **80**:39, 1904.

1904; Stühlern,[13] 1904; Apelt,[14] 1908; Brissaud,[15] 1912; Gouget and Moreau,[16] 1912; Mosny and Pruvost,[17] 1913; Sisson and Thompson,[18] 1915, and Zander,[19] 1919.

Although there were numerous reports up to 1915, Sisson and Thompson saw fit to include only thirty-three cases as completely studied and acceptable, to which group they added four. Since then a few complete studies have been made, which include a large series by Zander.

The bacteriologic observations have not been entirely constant. All observers have noted a gram-negative, round-ended, encapsulated bacillus growing with the production of a characteristic viscid diffluent growth. In carbohydrates of this organism the growth reactions resemble those of the colon-aerogenes group, but they vary from one to the other in the methyl red, Voges-Proskauer, lactose fermentations and milk coagulation reactions.

The clinical and pathologic aspects are most commonly those of an acute infection with the corresponding symptoms and observations. Most of the early reports dealt with such infections.

Apart from the acute infections, however, the micro-organisms have been isolated from conditions of the lungs of varying grades of chronicity, some extending over a period of months and years and simulating pulmonary tuberculosis or some other chronic disease of the lungs. Étienne included in his group one patient from Banti's and one from Galvagni's clinic, who lived for several weeks. Apelt [14] reported two fatal cases with large cavities, one undergoing a rib resection without avail. Cohn [20] reported one pulmonary abscess, but he did not state the outcome.

None of the older reports, however, conveyed the idea of chronicity that actually exists. In 1926, Belk [21] reported a series of eighteen cases, of which two and perhaps three were chronic abscesses of the lungs of long standing. In 1926, Westermark [22] was the first to call attention to the similarity of the condition to tuberculosis, as shown in

13. Stühlern: Zentralbl. f. Bakteriol. **36**:493, 1904.
14. Apelt: München. med. Wchnschr. **55**:833, 1908.
15. Brissaud: Lyon méd. **80**:205, 1912.
16. Gouget and Moreau: Bull. et mém. Soc. méd. d. hôp. de Paris **34**:296, 1912.
17. Mosny and Pruvost: Bull. et mém. Soc. méd. d. hôp. de Paris **35**:395, 1913.
18. Sisson and Thompson: Am. J. M. Sc. **150**:713, 1915.
19. Zander, A.: Deutsche med. Wchnschr. **45**:1180, 1919.
20. Cohn: Deutsche med. Wchnschr. **19**:804, 1893.
21. Belk, W. P.: J. Infect. Dis. **38**:115, 1926.
22. Westermark, N.: Acta radiol. **7**:626, 1926.

a case in which the patient lived for six months. The pathology and bacteriology were reported by Berglund.[23] In 1927, Brulé and his colleagues[24] reported one case of nine years' duration in which the disease fluctuated between a chronic condition of the lungs and periods of quiescence. In 1929, Collins and Kornblum[25] reported three chronic infections of the lungs by the Friedländer bacillus with recovery, all of which resembled tuberculosis. To this brief list of seven or eight cases we wish to add another.

The patient lived for twenty-eight months after infection, and presented the observations of chronic pulmonary abscesses simulating tuberculosis.

REPORT OF CASE

History.—W. K., aged 45, born in Poland, entered the sanitarium on Jan. 4, 1929. He had attended school for four years, had worked on a farm and had come to the United States at the age of 25. Since that time he had worked for a steel company. He smoked and drank with moderation. Except for slight colds and an operation for inguinal hernia, the past history was irrelevant. The present complaint dated from Sept. 28, 1927, when he "caught cold," following which he began to cough and to have a fever. There was a moderate expectoration that was sometimes blood-streaked, and the patient had lost 7 pounds (3.2 Kg.) in weight. His appetite was good; he slept and felt well, in spite of a rather severe productive cough.

Examination.—General inspection revealed a moderately thin man with a pinkish-white skin that differed from the usual pale yellowish complexion of the tuberculous patient.

The chest presented the principal positive observations: It was fairly symmetrical with a slight lag on the left; the expansion was poor; tactile fremitus was increased bilaterally, more posteriorly, and there was dulness in the upper lobe of the right lung. The breath sounds were diminished over the upper right and were slightly increased over the left. There were a few persistent râles in the upper lobe of the right lung. The diagnosis was "pulmonary tuberculosis, moderately advanced B."

There was a very small amount of sputum at this time, and the patient gained 5 pounds (2.3 Kg.) after admission.

The roentgen examination reported by Dr. Carroll E. Cook on Jan. 15, 1929, was as follows: The apexes of the lungs lighted up poorly, the left better than the right. The costophrenic angles were clear. The cardiac shadow was within normal limits as to size, shape and position. At the hilus on the right, and extending upward and outward, there were mottled areas of increased density with definite evidence of several cavities, typical of active, far advanced, pulmonary tuberculosis (fig. 1).

On three subsequent examinations the picture was essentially the same, with more extensive involvement and cavity formation each time (fig. 2).

23. Berglund: Acta radiol. **7**:626, 1926.

24. Brulé, M.; Huguenin, R., and Gilbert-Dreyfus: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1370, 1927.

25. Collins, L. H., and Kornblum, K.: Chronic Pulmonary Infection Due to the Friedländer Bacillus, Arch. Int. Med. **43**:351 (March) 1929.

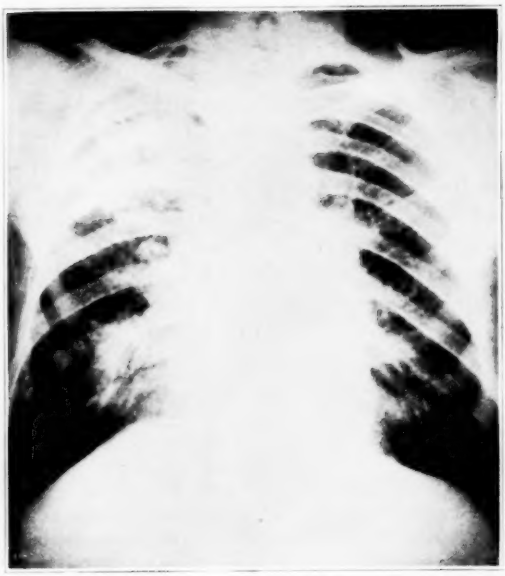

Fig. 1.—Roentgenogram of chest on admission, showing an involvement at the base of the right lung and cavities and infiltrations in the upper lobe of the right lung that are almost identical to a tuberculous process.

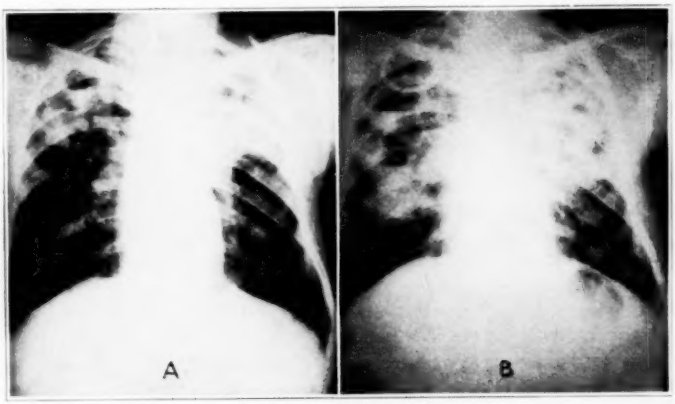

Fig. 2.—*A*, roentgenogram taken on Aug. 5, 1929, eight months after admission, showing more extensive excavations on the right with large annular shadows with fluid levels and extension to the upper lobe of the left lung. *B*, roentgenogram taken Dec. 2, 1929, two months before death, showing a still further progress of the disease. There is little to differentiate this from an advanced tuberculosis.

Clinical Course.—The patient improved until June, when he experienced a severe attack of coughing with pain in the chest, followed by profuse expectoration of a reddish-brown sputum containing peculiar brownish flakes. A persistent search for tubercle bacilli was negative. The odor was not offensive at this time. The cough was of a "brassy" type. Although following this attack there was evidence of extensive destruction of the lungs, the patient did not lose strength in proportion to the involvement, as occurs in tuberculosis. Even on the last day he was able to get up and brush his teeth. The physical signs also were not in proportion to the involvement shown by the roentgenogram. Toward the end the odor of the sputum became increasingly offensive. The temperature was very irregular, corresponding with what may have been septic exacerbations. Sometimes the pulse rate fell as the temperature rose, although not always.

The most important laboratory observations were the continued absence of tubercle bacilli in the sputum in six guinea-pigs, many cultures and more than eighty direct examinations, as well as the persistent finding of a heavy, mucoid, encapsulated bacillus that was tentatively considered a member of the *B. mucosus-capsulatus* group. Urinalysis gave negative results, and the blood revealed only a moderate leukocytosis (13,000) with a mild anemia.

The patient died on Jan. 31, 1930, and a necropsy was performed within seven hours.

Necropsy Observations.—The essential features observed were as follows: The body was that of a markedly emaciated white man, aged 46, 5 feet, 3 inches (160 cm.) in height, weighing 105 pounds (47.6 Kg.). Postmortem rigidity was present, and lividity was seen in the dependent portions. The pupils were equal and measured 5 mm.

The following observations were made on the thoracic cavity and lungs: The pleural cavities were completely obliterated by firm fibrous adhesions, except at the bases. In the lower right side of the pleural cavity there was about 500 cc. of a foul-smelling, greenish-yellow pus. The heart lay in the midline and was about the size of the patient's fist. The tracheobronchial lymph nodes were enlarged, and on cut section were grayish black, but showed no evidence of tuberculosis.

On section, the upper lobe of the right lung contained a large cavity toward the axillary angle, measuring 5 by 7 cm. The wall was grayish black and did not appear to possess the usual type of granulation tissue found in tuberculosis. The fibrous capsule over the apex was from 2 to 3 mm. in thickness, and was perforated in a few places. Anteriorly this cavity communicated in a downward direction with a cavity on the anterior surface of the middle lobe. There was also a cavity in the lateral angle in the middle lobe, measuring 3 by 5 cm. There was a small early cavity in the inner border of the middle lobe that was in the process of formation, measuring 1.5 cm. in diameter. In the lower lobe there were a few early cavities in the anterior portion with slight atelectasis toward the base, resulting from compression by fluid. There was an occasional infiltration of the secondary lobules ranging from small, early, grayish consolidations to larger areas of caseous bronchopneumonia with reddish central portions. Throughout the cut surface of both lungs there were numerous deposits of coal pigment measuring 3 mm. in diameter and spaced about 7 mm. apart.

The upper lobe of the left lung contained a large irregular cavity extending from the anterior through to the posterior aspect and measuring at different diameters from 8 to 10 cm. across. It was partially filled with a grayish-pink, gelatinous pus. The lower lobe contained a few smaller cavities in the upper part, measuring from 1.5 to 2 cm. toward the apex and decreasing in size toward

the middle of the lower lobe, where there were a few that measured from 7 to 10 mm. A few consolidations were present, as in the right lung. The base of the left lung was relatively normal (fig. 3).

The microscopic appearance of the lesions from the different parts of the lungs was as follows: An early lesion from the lower lobe of the right lung showed many alveoli filled with scattered fibrin shreds containing a few lymphocytes, monocytes, red cells and coagulated serum, undergoing varying stages of resolution with a superimposed necrosis. The fibrin was irregular in location. The centers of necrosis began at irregular intervals throughout the nodule and coalesced as the alveolar walls were broken down. The cellular content varied,

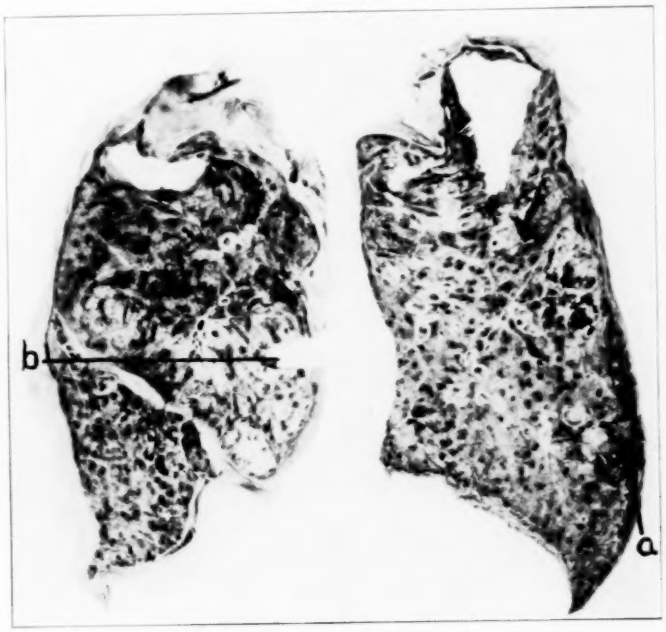

Fig. 3.—Sagittal section of both lungs anterior to the bronchi, showing large cavities with partially epithelialized walls and smaller thin-walled cavities. The two small sections (*a*) and (*b*) have been removed from small foci of bronchopneumonia, which are represented in figures 4 and 5.

the majority of the nodules consisting of lymphocytes and plasma cells. Most of the blood cells in the alveoli were laked, and the vessels appeared engorged, bright red and homogeneous. In the older necrotic centers there were more polymorphonuclears, increasing in some parts to 75 or 80 per cent of the cellular content, and appearing like acute miliary abscesses superimposed on the more chronic lesions (figs. 4 and 5).

A moderately advanced lesion showed the walls of the alveoli broken through and most of them destroyed by necrosis; irregularly throughout the margin of the lesion there were layers of fibrin with only a few cells and laked red blood

cells packed within the remaining alveolar walls. Early ulceration was present in the interior. The border of the lesion was sharply demarcated from the surrounding lung tissue.

An advanced lesion showed the walls of the larger cavities in the upper part of the lower lobe composed of an irregular wall of granulation tissue, beneath which were burrowing miniature abscesses composed chiefly of leukocytes varying in the percentages of each variety in different locations. As a whole, the early formations were nearly all lymphocytes, but polymorphonuclears seemed to come later, and appeared to hasten the necrosis and ulceration.

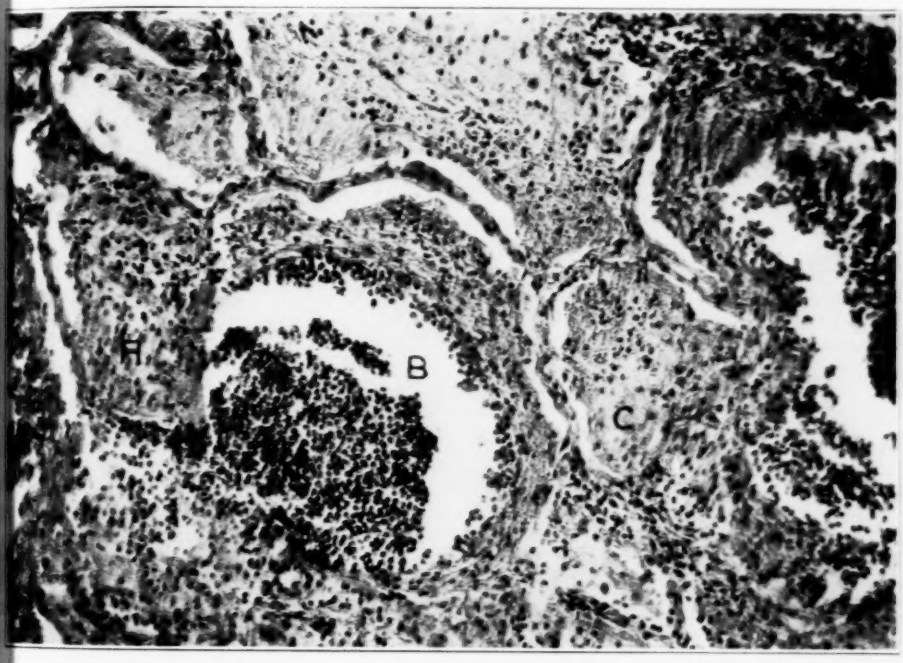

Fig. 4.—A high, dry, microscopic field of a bronchopneumonic focus, showing the beginning of the stage corresponding to gray hepatization. Some alveoli at *A* were filled with a thin material containing scattering monocytes and a few fibrin shreds. At *B* is an alveolus in which an infiltration of lymphocytes and polymorphonuclears has begun along the alveolar wall and has extended into the center of the mass. The alveolar wall shows a beginning disintegration at *C*. Hematoxylin and eosin stain; reduced from × 240.

In a section of the wall from the inner to the outer border of the cavity there was a layer of loose débris composed of broken down cells of all types (polymorphonuclears, lymphocytes, monocytes, "foam cells," etc.) and fibrin. Beneath this was a layer of granulation tissue about 0.5 mm. thick, the inner border of which was necrotic and protruded in some places into polypoid projections which had layers of squamous epithelium over them in some places, and cuboidal or

columnar epithelium in others. In this layer were newly found blood vessels, some of which were engorged and apparently undergoing thrombosis. Many lymphocytes, a few polymorphonuclears, fibroblasts and more adult connective tissue were also present. Beneath this layer was a layer about 0.5 mm. in thickness of compressed and extinct alveoli, with heavy strands of pinkish-stained connective tissue. In and beneath this layer were cells of all types: desquamated alveolar cells, "foam cells," phagocytes containing coal and iron pigment, with a blending into the abscesses described. Emphysematous blebs were occasionally present. The arterioles were undergoing endarteritis. On oil-immersion examination, many

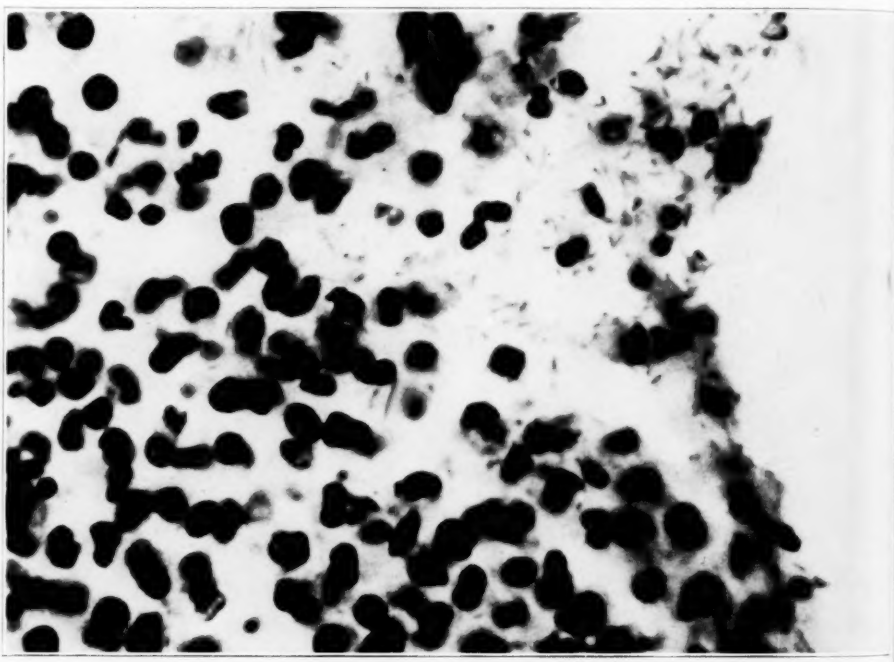

Fig. 5.—A high power view of the edge of a slough, showing polymorphonuclears and monocytes containing a few bacilli and numerous free bacilli. Gram stain; reduced from × 1,450.

round-ended bacilli could be seen, a few of which were observed within polymorphonuclears and monocytes. They had thick capsules when found within the monocytes and appeared like vacuoles containing bacteria (figs. 6 and 7).

The bronchi draining the larger cavities and leading to the new foci had a mucosa that showed varying degrees of ulceration. In some places the mucosa was entirely denuded, with an infiltration of the submucosa with lymphocytes and only a few polymorphonuclears. A Gram stain of the section revealed numerous large gram-negative bacilli throughout the lesions. An acid-fast stain was negative for acid-fast bacilli.

The bacteriologic observations were of equal interest.

While examining specimens of sputum, one could not help observing many heavily encapsulated bacilli with rounded ends. This micro-organism was present in the sputum in an almost pure culture, and there was no difficulty in isolating it. The same organism was isolated from the urine of the patient just a day before death, and once directly from the abscess of the lung at the postmortem examination.

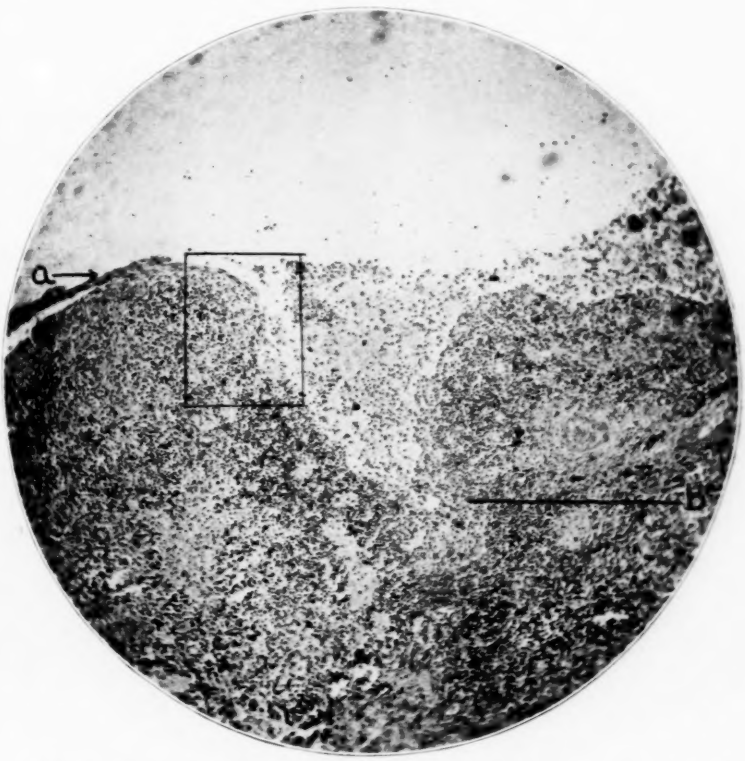

Fig. 6.—The wall of a large cavity, showing a simultaneous regeneration of epithelium by metaplasia at *a* and abscess formation at *b*. Hematoxylin and eosin stain; × 69.

The micro-organisms isolated from the sputum, urine and abscesses of the lungs were identical in every respect. The cultural studies were made from a single colony fished from a twenty-four hour lactose plate.

The fermentation of carbohydrates was studied on agar slants containing 1 per cent of the carbohydrate and the double indicators—bromcresol purple and cresol red. It fermented arabinose, rhamnose, xylose, dextrose, galactose, levulose, lactose, maltose, sucrose, salicin, glycerin, mannitol, sorbitol and adonitol, with

acid and gas, both aerobically and anaerobically. Raffinose and starch were fermented only in the butt aerobically, but throughout anaerobically. Dextrin, inulin and dulcitol gave negative reactions.

It is interesting to note not only that the micro-organism grows as well anaerobically as aerobically, but that the reactions in carbohydrates were found to be more pronounced while the organism was growing in anaerobic conditions. This was especially noticeable in the beginning. Other details of the biology of this micro-organism were as follows: The Gram stain was negative. The growth on agar slants was very mucoid, stringy and almost diffluent. Litmus milk was acidified within from eighteen to twenty-four hours, and coagulation took place

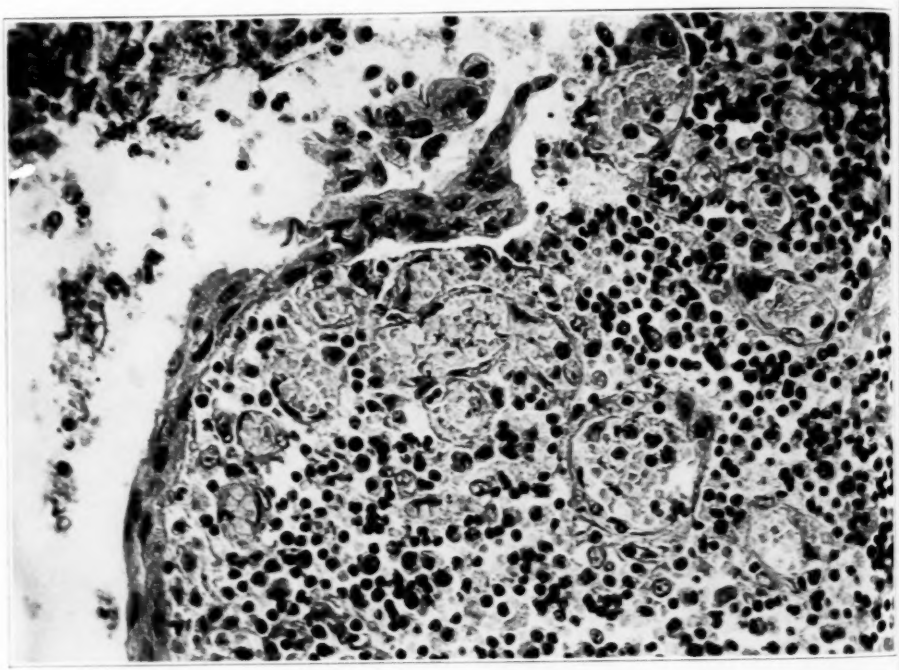

Fig. 7.—A higher magnification of the metaplasia of epithelium, showing the field outlined in the rectangle in figure 6. Hematoxylin and eosin stain; reduced from × 470.

after forty-eight hours. Indol was not produced. Nitrates were reduced to nitrites. Urea was not decomposed. The methyl-red test gave positive results. The Voges-Proskauer test gave negative results. Citrate was utilized. These last three tests were repeated eight times, always with the same results. Gelatin was not liquefied. The growth had a typical "nailhead" appearance. Hydrogen sulphide was not produced.

The motility was studied with broth cultures. Examination of hanging drops was made after eight, twelve, fifteen and eighteen hours of incubation, and all of the tests gave negative results.

Capsules were easily seen in the specimens of sputum with the methylene blue (methylthionine chloride, U.S.P.) stain. However, while the properties of this organism were studied, it was grown on milk agar slant for eighteen hours, and was then examined for the formation of capsules by the india ink method. With this preparation wide capsules were observed. Hemolysis was not produced. Growth appeared within twenty-four hours on potato, but growth was poor on this medium. There was no formation of gas.

Pathogenesis.—Mice, rats, guinea-pigs and rabbits were inoculated with broth culture. The mice died within from thirty-six to forty-eight hours after the subcutaneous injection of 0.1 cc. Subcutaneous injection of 0.5 cc. killed rats within three days. An intraperitoneal injection of 1 cc. killed guinea-pigs within thirty-six hours, while on subcutaneous injection only local abscesses developed, which ultimately healed. Intravenous injection, it seems, is only slightly pathogenic for rabbits.

Cultures from the heart's blood of mice, rats and guinea-pigs always yield a luxuriant growth of gram-negative bacillus, identical to the one that was inoculated.

Pathologic Observations.—The pathologic condition in mice and rats was similar. There was an extensive edematous infiltration for 1 or 2 cm. around the needle puncture. The peritoneal cavity contained a mucoid pus. There were miliary abscesses in the liver and kidneys; the spleen was slightly enlarged and dark red. The lungs were hemorrhagic, but not consolidated. There were cystitis and pyelitis.

From the various observations we were able to give an abbreviated anatomic diagnosis, as follows: chronic multiple pulmonary abscesses of both lungs with progress toward the base, presenting various stages of evolution from small foci of bronchopneumonia to large, thick-walled cavities, produced by encapsulated micro-organisms belonging to the Friedländer bacillus group; empyema of the right pleural cavity, with fibrinous pleuritis and atelectasis of the base of the lungs; obliterative pleuritis of the apexes of both lungs. Other incidental observations were: hypertrophy and the deposit of coal pigment in the tracheobronchial lymph nodes; brown atrophy of the heart; slight fatty changes and marked passive congestion of the liver, spleen and kidneys; cloudy swelling of the liver and kidneys; acute splenic tumor; slight hyperplasia of the thyroid and atrophy of the prostate and right testis.

COMMENT

The feature of the case reported is that it represents a chronic type of infection with Friedländer's bacillus, which may be represented by a series of infections ranging from one day to many years. It seems logical, therefore, to follow the time-honored system of dividing the process into acute and chronic phases.

In order properly to understand the latter, it will be of advantage to detail the important observations in the former. The most complete work on the acute disease has been done by Moïsejew, Kokawa, Stühlern, Brissaud and his colleagues, Apelt, and Sisson and Thompson, among others, each group of which reported a series of cases. Some of their observations will be described, especially the pathologic ones.

In 1900, in reporting five cases, Moïsejew [10] compared this type of pneumonia to the three stages of croupous pneumonia, and showed striking and characteristic differences. This form begins without a true stage of red hepatization. Although a few fibrin plugs and red blood cells may be present, the cut surface is generally gray, semitransparent, nongranular and viscid from the beginning, owing to the masses of encapsulated bacilli and thick mucoid capsules. On fresh section, there is a "burnt-meat" odor. Secondary foci of hepatization arise from the primary, and undergo the same stages of evolution, which have the following characteristics: the alveoli are dilated, with a granular edema containing scanty fibrin, scattering leukocytes and "alveolar cells" (monocytes) with many bacteria in their protoplasm. The blood vessels are engorged, especially on the periphery of the hepatization. Some alveoli contain blood. In the next stage, corresponding to the stage of gray hepatization of croupous pneumonia, the gray centers are due to the leukocytes invading the alveoli, usually along the walls, leaving the central mucoid mass. The blood vessels become constricted, and the alveolar walls become infiltrated with leukocytes. Necrosis finally develops, owing to this avascularity. In the red peripheral zone, the alveoli are of different sizes, and contain a recent cellular exudate, bacteria, mucoid masses and red blood cells. The alveolar walls are thinner and contain less leukocytes, but the capillaries are filled with blood that becomes coagulated and plugged with fibrin, and ultimately form solid thrombi that lead to necrosis, hemorrhage and abscess. This corresponds to the state of resolution of croupous pneumonia.

In 1904, Kokawa [12] reported work on fourteen cases, nine of which were complete. Although his observations differed from those of Moïsejew in certain features, there was a common likeness. Kokawa stated that the cut surface is granular. As a general rule, there is less fibrin than in ordinary pneumonia, but there are still enough fibrin plugs to give a granular appearance in places, but not enough to give it the appearance of lobar pneumonia. He described the irregular position of the fibrin around the walls of the alveoli and through the "pores." He also emphasized the red coloration more and perhaps gave a more comprehensive idea of the condition, due, no doubt, to his greater amount of material.

In 1912, Brissaud and his colleagues [13] reported nineteen cases and added little to what had been given before. They grouped the cases in three groups, namely: those like true lobar pneumonia; those like confluent bronchopneumonia, and, the most common, those that are called pseudopneumonia, in which a large part or all of a lobe may be involved as one focus, but in which the borders are irregular and distinct from a lobar process. These authors expressed the belief that the observations are rather specific and characteristic.

In 1915, however, Sisson and Thompson,[18] in reporting four cases, said that they thought that no one feature may distinguish this form of pneumonia from the pneumococcus type, yet certain characteristics taken together will make the process easy to recognize. Their observations in general agree with the others mentioned.

From a clinical standpoint the disease is not so definite. Brissaud cited Letulle and Lumière, who divided it into two clinical groups: (1) atypical "pseudopneumonia," as previously described, and (2) like typical pneumonia, with recovery (Wiens, Schmidt), following surgical intervention and recovery (Lenhartz), or, more commonly, by death.

The physical findings reported are meager; Weill[26] and his co-workers reported the findings only of engorgement with absence of flatness, breath sounds and subcrepitant râles. These atypical observations are due no doubt to the mucoid material that obstructs the smaller air passages. The same author reported that the involvement shown by roentgen shadows is not the triangles typical of pneumonia, but is more circumscribed.

The clinical course of the disease is often characteristic. There are usually a sudden onset and a rapid course (from two to five days), and usually there is no chill or herpes labialis. The temperature is usually irregular; there are a profound intoxication, cough, pain in the side and a pinkish-brown sputum containing encapsulated bacilli within and without the monocytes. Dyspnea is a constant, grave symptom. Death comes suddenly. The opinions of many physicians may be summarized in the words of Sisson and Thompson, who said that "General weakness, coma, signs of cardiac and respiratory failure all come suddenly and are outspoken. The frequency of the various lobes involved is of little importance. The outcome is nearly always fatal, death coming with little premonition."

Some authors, namely Netter, quoted by Étienne (twelve cases), Brissaud (nineteen cases) and many others, considered it always fatal. Lord[27] said that in no established case had the patient ever recovered. On the other hand, Zander[11] reported an epidemic in which only 35 per cent of the patients died. This report is striking in that the disease assumed epidemic proportions, and for that reason should be looked on in a different light than the sporadic unfavorable cases in which the mortality rate is very high. Therefore, it does not seem justifiable to consider every case of Friedländer's pneumonia as fatal because the early complete reports are on fatal cases. It is not consistent with

26. Weill: Lyon méd. **122**:133, 1914.

27. Lord: Diseases of Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, 1915, p. 234.

the epidemiology of the disease, and besides many recoveries are not studied or even suspected. As we have mentioned, many cases become chronic, and in some the patients are reported to have recovered.

The chronic type of infection, the one about which we are most concerned in this report, is relatively less common. It is variable in its course. The clinical and pathologic manifestations vary from the acute form previously described to a chronic fibroid disease of years' duration. Many authors speak of a tendency toward the formation of abscesses, but references to such a symptom are not common in cases in which complete work has been performed. Only the relatively recent work is sufficiently complete to give a clear idea of the type of chronicity assumed by some of these infections.

In 1926, the cases of Belk [21] were completely recorded, except that no protocols were given to show the type of micro-organisms present further than a "Friedländer bacillus." He mentioned one important characteristic that is omitted by most authors; namely, that the abscesses are not foul-smelling. This is true at the beginning. Moïsejew and others mentioned an odor of burnt meat in the fresh specimen, but the chronic lesion seems to have little odor until late in the disease.

In the case of Westermark, reported by Berglund, there was a relatively complete bacteriologic and pathologic report. From this patient a micro-organism was isolated from a prostatic abscess. It produced an abundant, yellowish-gray, glassy growth on potato. The author did not mention the formation of gas. Dextrose bouillon is the only sugar mentioned, and that sugar produced acid and gas. There was a typical nailhead growth on gelatin. It was pathogenic to mice, rabbits and guinea-pigs intraperitoneally, but one rabbit survived subcutaneous injection. The dosage was not stated. Other culture reactions are characteristic or are not reported, which is true for the Voges-Proskauer and methyl-red reactions.

The gross pathologic changes were rather characteristic of a confluent bronchopneumonia with abscess formation. Microscopically, the alveoli contained an exudate consisting of polymorphonuclears, "alveolar epithelium" and a few lymphocytes. There was a thin network of fibrin, and in places there were many red blood corpuscles. Many alveoli contained masses of encapsulated bacteria. The alveolar walls were destroyed in places, and only leukocytes, bacteria and mucus were found. The walls of the cavity consisted of well differentiated bundles of collagen-bearing connective tissue. No remnants of bronchial walls could be found in the walls of the cavity. There was no evidence of tuberculosis. This report resembles ours, so far as the data given are concerned.

In 1927, Brulé, Huguenin and Gilbert-Dreyfus [24] reported a case that began with a chill, pain in the side, dyspnea, elevation of temperature,

cough and expectoration of a greenish sputum several times a day. The condition gradually became worse, the sputum became bloody, and the course extended over a period of nine years with numerous remissions. A rather characteristic Friedländer's bacillus was isolated, a vaccine from which seemed to help somewhat, but the improvement was not permanent. On physical examination during the patient's last illness, a normal percussion note was observed; the right side was painful on palpation and dry râles were noted on the left side opposite the vertebrae and at the base with a bronchial souffle at the apex. On the right there were rhonchi that changed to sonorous râles on subsequent examinations. Patches of fine râles were heard at certain places. Roentgen observation showed a uniform gray on the left, and a brushlike shadow at the base of the right lung, which suggested bronchial dilatation. The upper lobes were opaque, but not homogeneous, with a gray apex and a dark shadow beneath, which without careful roentgen observation would be considered an incisural lesion.

The gross pathologic observations revealed lesions of a chronic cirrhosis of the lungs with dilated bronchi and cavities blending into acute foci of bronchopneumonia. Microscopic lesions were characterized by peribronchial fibrosis with numerous lymphocytes and plasma cells. The epithelium was normal, flat or in layers showing true metaplasia. In the fibrotic apex of the right lung there was marked vascular and parenchymal sclerosis with lymphocytes, plasma cells and miliary foci of polymorphonuclears. The lesions appeared in crops or "échelons."

Collins and Kornblum [25] discussed the acute type in which death intervenes within from twenty-four to forty-eight hours, and reported three cases of the chronic type. The roentgen observations showed lesions of bronchopneumonia that were gradually coalescing to form pseudolobar pneumonia. It differed from the lobar form in not being so dense; it was not limited to one lobe, and was more intense at the periphery. The cavities were thin-walled and differed from those seen in any other condition except perhaps in chronic influenza. In the healed cases there was marked fibrosis. The authors divided the process into four stages: bronchopneumonia, pseudolobar pneumonia, abscess formation and fibrosis. They believed that the chronic process should be considered a disease entity.

Bacteriologically, the micro-organism that we isolated did not correspond in every way to the usual type of Friedländer's bacillus. The typical mucoid growth on agar, the presence of large capsules, the inability of the organism to liquefy gelatin or to produce indol and the source from which this organism was isolated suggested that it is closely related to *B. pneumonia* of Friedländer. There is, however, considerable controversy as to what should be considered a typical strain

of Friedländer's bacillus. Many authors (Strong [28] in 1899, Perkins [29] in 1904, Howard [8] in 1898, Wilde,[30] and Coulter [31] in 1917) described the typical strain as lactose-negative, while others (Grimbert [32] in 1896, Nicolle and Hebert [33] in 1897, and Topley and Wilson [34] in 1929) considered it capable of fermenting lactose with acid and gas, and there are still others (MacConkey [35] in 1905, and Castellani and Chalmers [36] in 1919) who reported acid but no gas in lactose. Authors who considered the typical strain of *B. pneumonia* of Friedländer to be lactose negative reported it also as not capable of producing coagulation in milk. Our strain constantly produced acid and gas in lactose, and coagulated milk within forty-eight hours.

Then it is not clear whether a typical strain should be methyl-red negative and Voges-Proskauer positive, or vice versa. There are disagreements on this point among certain authors. Our strain gave a positive reaction to the former and a negative one to the latter. It also utilized citrate, which is unusual for a strain that does not give a positive reaction to the Voges-Proskauer test. However, the last observation is in accord with the observation of Edwards,[37] who stated that the relation of the methyl-red and the Voges-Proskauer tests to citrate, which usually exists in the *B. coli-acrogenes* group, has not been demonstrated with strains of encapsulated bacilli from human sources.

In conclusion, infections by the Friedländer bacillus should be considered chiefly from the standpoint of a rather extraordinary parasite. The most important factors seem to be: (1) the large number of bacilli with their heavy mucoid capsules that act as a foreign body and are difficult to cope with and (2) what appears to be a toxin of variable but undoubted potency. As a result, the different strains possess different degrees of virulence for each host, and, owing to this difference no doubt, the disease runs a fulminating, a subacute or a chronic course.

All of the various types of the disease (lobar, confluent lobular, lobular or "pseudo" pneumonia) present the same general observations with

28. Strong: Centralbl. f. Bakteriol. **25**:49, 1899.

29. Perkins: J. Infect. Dis. **1**:241, 1904.

30. Wilde: Centralbl. f. Bakteriol. (pt. 1) **20**:681, 1896.

31. Coulter, C. B.: J. Exper. Med. **26**:763, 1917.

32. Grimbert: Ann. de l'Inst. Pasteur **9**:840, 1895; **10**:708, 1896.

33. Nicolle and Hebert: Ann. de l'Inst. Pasteur **9**:67, 1897.

34. Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, New York, William Wood & Company, 1929, vol. 1, p. 461.

35. MacConkey: J. Hyg. **5**:333, 1905.

36. Castellani, N., and Chalmers, J. E.: Manual of Tropical Medicine, London, Ballière, Tindall & Cox, 1919, p. 934.

37. Edwards, P. R.: J. Bact. **15**:245, 1928.

only two variable factors, namely, the extent and the age of the lesions. The typical course of the lesion, whether it is a small lobule or a whole or a part of a lobe, is an invasion of the mucoid bacilli into the bronchioles and alveoli, with the prompt exudation of a thin fluid containing scanty fibrin and a moderate number of monocytes that promptly begin to engulf the bacilli. These phagocytes appear stuffed with the vacuoles of mucus that coalesce as the bacilli are destroyed. The alveolar blood vessels then become engorged with red blood cells, and some of them rupture in places, leaving scattering red corpuscles. This corresponds to the red stage of hepatization in pneumococcus pneumonia. It rarely has an appearance of a true red hepatization, but is a more smooth, slimy, yellowish gray, with a dark red zone where the blood vessels are engorged and ruptured. The red color is due to the engorged blood vessels, the true hemorrhage and the scattering fibrin, and not to the extensive fibrin and extruded red blood cells as in pneumococcus pneumonia. Following this "red" stage is what corresponds to the gray stage in which polymorphonuclears infiltrate along the alveolar walls and penetrate the alveolar plugs as well as the alveolar walls, where a tremendous dilatation of the vessels occurs, followed by thrombosis and an impairment of the circulation. This stage is then followed by resolution, which more frequently terminates in necrosis with sloughing, hemorrhage and the formation of abscesses and cavities. In the extremely acute infection this process may extend over the whole lobe at nearly the same time, with death intervening before the gray stage is developed. This is represented by the true lobar types. The more slowly developing lesions occur not only in crops of different ages (lésions en échelons) but they have zones of different ages within the individual lesion from the center to the periphery as the lesions spread. There are usually all stages existing in the same patient and in the same lesion. The varying grades of chronicity then ensue with polymorphonuclears, and the gradual substitution of lymphocytes, plasma cells, fibroblasts, fibrous tissue and epithelialized cavities, as described before.

SUMMARY

The clinical course and the pathologic and bacteriologic observations of a fatal, chronic infection with Friedländer's bacillus are described. The micro-organism differed from that ordinarily described, in that it grew as well or better anaerobically as aerobically, it grew poorly on potato medium, it fermented lactose with acid and gas, and it produced coagulation in milk.

The pathologic condition was that of a subacute to chronic bronchopneumonia with progressive necrosis and abscess formation exhibiting

a varied type of cell reaction that varied from lymphocytes, monocytes and plasma cells to focal abscesses of polymorphonuclears.

Fibroblasts and connective tissue appeared about and within the older lesions, and the walls of the cavities became lined with metaplastic cuboidal or squamous epithelium. An important feature of the disease is the continuous succession of lesions, usually from the apex to the base of the lung, each of which passes through the same evolution and changes from the acute (described by Moïsejew, Kokawa and others) to the chronic form already outlined.

The clinical aspects closely simulated chronic pulmonary tuberculosis, differing from it only in the general appearance of the patient, the irregularity in temperature and the obscure physical observations. The roentgen observations resemble those noted in chronic pulmonary tuberculosis.

STREPTOCOCCIC SEPTICEMIA WITH VASCULAR LESIONS *

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This report of a case of streptococcic septicemia, presenting an unusual clinical course and at autopsy showing a vascular lesion in several organs, merits careful consideration.

REPORT OF A CASE

History.—A Negro, aged 32, entered the hospital with the sole complaint of pain in the lower portion of the back. He believed himself to have been in perfect health until three weeks before admission, when, while at work, he lifted some heavy metal and experienced a sudden, severe pain in the lower portion of the back. The persistence and radiation of the pain were characteristic of acute strain. The only additional symptom was nocturia two or three times, which the patient insisted had commenced subsequent to the injury.

The past history was unimportant except for several attacks of tonsillitis covering a period of years, gonorrhea eighteen years, and trauma to the right knee eight years, before the present examination. It is of considerable interest that this man did general work in a brass factory where, much of the time, he handled objects weighing 100 pounds (45.4 Kg.) or more without experiencing any symptoms.

Examination.—Physical examination on admission to the hospital, three weeks after the onset of pain, showed persistent tenderness over both sacro-iliac joints and the lumbar muscles, which confirmed the obvious diagnosis of acute strain of the back. This condition responded promptly to orthopedic measures, and became entirely negligible within a few days.

Complete physical examination showed a very black Negro of excellent physique, sitting in bed without distress. He was mentally alert and cooperative. The temperature was 99 F., the pulse rate 90 and the rate of respiration, 20. The upper and lower teeth were much diseased and partially destroyed. The tonsils were moderately enlarged and, together with the pharynx, were swollen and diffusely injected. The left tonsil was covered with a thin, whitish exudate. A few, small, nontender, cervical glands were palpated. The lungs were normal.

In the examination of the heart, the apex impulse was seen and felt in the fifth space inside the nipple line. A rub was felt over the lower part of the precordium to the left of the sternum. The left and right borders and the area of supracardiac dulness were not increased on percussion. At the apex, the first sound was loud, became accentuated and passed into a harsh systolic murmur,

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The weak second sound was followed by a definite pause and then later in the cycle by the appearance of a low-pitched diastolic murmur. At the base, the pulmonic second sound was greater than the aortic. A soft systolic but no diastolic murmur was heard. The precordial rub was audible in the area over which it was felt. The heart was rapid, at this time 120, but perfectly regular. The blood pressure was 118 systolic and 90 diastolic. Palpation of the abdomen was unsatisfactory owing to voluntary spasm, but, at a subsequent examination, the spleen was definitely felt. On the basis of these observations, a tentative diagnosis of rheumatic heart disease, pericarditis, mitral stenosis and questionably active endocarditis seemed justified.

The laboratory studies of the blood were consistent with the diagnosis of a rheumatic vascular process. The Wassermann reaction was negative. The red blood cells were 2,400,000 with 50 per cent hemoglobin, and the white blood cells were 6,300 with a differential count of polymorphonuclears, 78 per cent; lymphocytes, 14 per cent; transitionals, 6 per cent, and eosinophils, 2 per cent. The red cells showed moderate anisocytosis but no other feature. An essentially similar blood picture was obtained four days later, although the white count on this occasion was 9,000. *Streptococcus viridans* was readily cultivated from the blood stream. An electrocardiogram showed: low potential in all leads especially I and III; the rate, 100; the rhythm, regular; P-R interval, 0.15; R diphasic in leads II and III, and high T complexes in leads II and III. The observations of the urine were, however, unexpected. Three examinations gave specific gravities of from 1.013 to 1.015; a heavy trace of albumin; from 10 to 35 red blood cells per high power field; from 3 to 12 white blood cells per high power field, and from 1 to 10 granular casts per low power field. Phenolsulphonphthalein dye was not eliminated in two hours and ten minutes on two tests made three days apart. The Mosenthal test showed marked fixation in the urine of both gravity and volume, with an increase of volume at night over that during the day. In five of the nine specimens, the specific gravity was 1.015; in three, 1.014, and in one of the specimens collected at night it was 1.012. These observations of the urine were supported by chemical analysis of the blood which gave nonprotein nitrogen, 162; creatinine, 8.8, and carbon dioxide-combining power, 32.

Course.—The clinical course during the first two weeks of the patient's stay in the hospital of eighteen days proved uneventful. The patient was symptom-free and, since his back was better, insisted that he should be up and about. The clinical chart showed a maximum temperature of 100.4 F. on two occasions at the time of entrance, and no other observations above 99.8 F. in spite of a throat which was obviously inflamed for several days. The rate of the pulse varied from 105 to 86 during the first week and after that remained between 68 and 92. The blood pressure increased slightly from 118 systolic and 90 diastolic to 126 systolic and 94 diastolic. However, the daily cardiac examinations showed considerable variation in the location and intensity of the rub and of the murmurs.

The death of the patient was as rapid as it was unexpected. Four days before death, he complained of slight nocturnal dyspnea. Obvious dyspnea appeared only two days before death, but the patient remained alert and made no complaints although he was not as energetic as previously. The acute stage lasted less than eighteen hours. The dyspnea increased, he became irrational, and his great strength seemed to melt away. The pulse did not vary significantly, although the temperature became subnormal. The blood pressure rose slightly to a maximum of 136 systolic and 90 diastolic. As the coma increased respiratory distress was the predominant feature. The terminal picture was typical uremia.

Autopsy.—Autopsy was performed four hours after death. As the interest centers chiefly around the heart and kidneys, a report of the detailed gross and microscopic examinations of these organs are given.

The heart showed moderate hypertrophy of the left ventricle. The subepicardial zone of the wall of the left ventricle showed a great many pale yellow or yellowish-white, firm patches, most of which were indistinctly circumscribed. Sclerosis of the mitral valve together with its chordae tendinae was present. Several groups of minute, pinkish-gray excresences were present along the line of closure of the mitral valve with considerable hemorrhagic infiltration of the adjoining valvular substance. There were no gross lesions of the remaining valves.

On microscopic examination, the mitral valve was found to be the seat of a chronic productive inflammatory process with marked vascularization of the valvular substance. The latter contained groups of large mononuclear and, in places, syncytial cellular elements. These cells were hardly distinguishable from the cellular constituents of the typical Aschoff bodies which were present in the myocardium. However, their nodular arrangement was far less pronounced in the valve than in the muscle of the heart. Many of the smallest vessels of the valve showed an advanced stage of a chronic productive endovasculitis leading to partial obliteration of the lumen. Along the line of closure of the valve, numerous more or less focal subendothelial accumulations of mononuclear, presumably histiocytic, cells were seen. The centers of many of these accumulations of cells showed areas of necrosis, including the surface endothelium, although in many instances not covered by thrombi (fig. 1). In the areas showing a more advanced stage of the active endocarditic process, the superficial valvular substance was partly replaced by broad bands of a homogeneous acidophilic material which blended imperceptibly into the adjoining deeper collagenous fibers (fig. 2). In view of this behavior and of the fact that this homogeneous material did not extend into the overlying thrombi, but ended sharply in lines continuous with the adjoining endothelium, it appears reasonable to look on it as the result of a "fibrinoid" degeneration of the valve (Neumann [1]) rather than as a penetrating thrombus in the sense of Ribbert.[2]

The myocardium was the seat of a moderate number of distinct, large, cellular nodules which, in many instances, showed the typical architecture of the Aschoff body. Here and there, foci of a similar cellular composition but lacking the distinctive nodular arrangement were found. These areas were most numerous in the subendocardial zone and in the vicinity of the medium-sized arterioles. The yellowish subepicardial patches, seen on gross examination, were found to correspond to areas of anemic necrosis of the muscular substance. The necrotic areas were composed of the supporting connective tissue, but with fragments of muscular substance and red blood cells scattered throughout. Evidences of an inflammatory nature of this process were lacking. Therefore, these areas might reasonably be interpreted as recent anemic infarcts such as are frequently seen in cases of coronary sclerosis. However, neither gross nor microscopic evidence of coronary sclerosis was found. On the other hand, numerous arterioles throughout the myocardium showed a lesion of predominantly alterative character. At intervals, subendothelial accumulations of a homogeneous, acidophilic substance

1. Neumann, E.: Virchows Arch. f. path. Anat. **144**:201, 1896.

2. Ribbert, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 2, p. 216.

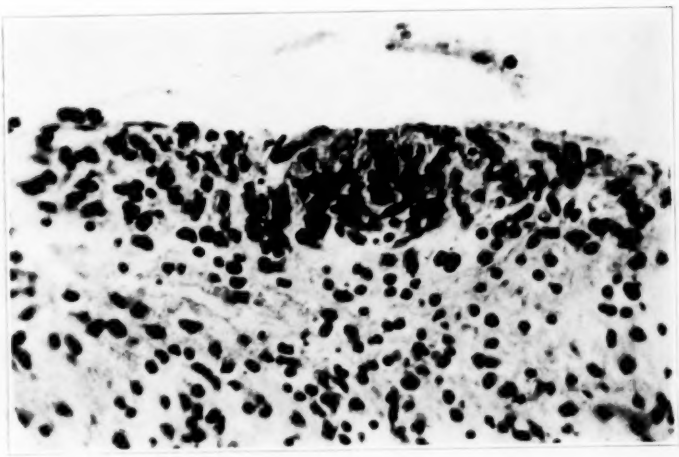

Fig. 1.—Mitral endocarditis with large cellular proliferative reaction and superficial necrobiosis; (Leitz "Makam:" magnification × 320).

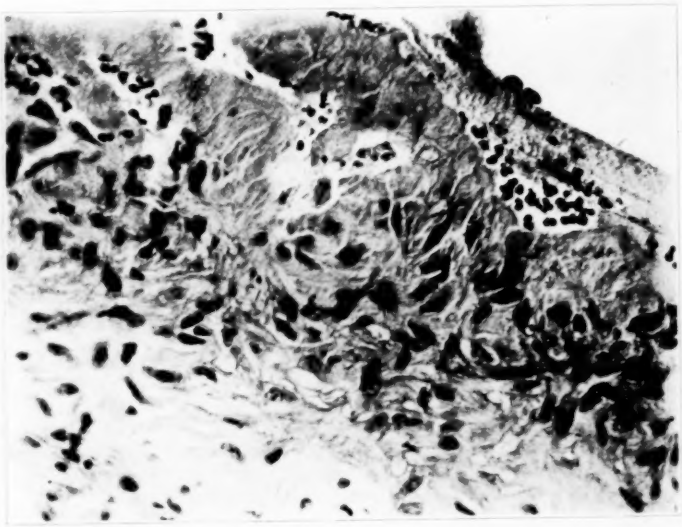

Fig. 2.—Mitral endocarditis with large cellular proliferation "fibrinoid" degeneration of the endocardial substance and thrombosis; (Leitz "Makam:" magnification × 320).

protruded into the vascular lumen in a button-like manner. The appearance of this material closely resembled that of the homogeneous bands which were encountered in the advanced lesions of the endocardium (fig. 2). In some of the larger arterioles, part of the media appeared to be replaced by this material. A moderate number of arterioles were practically obliterated by the subendothelial accumulation of this homogeneous substance in association with some proliferation of the endothelium (fig. 3). Since coronary sclerosis was not present, the anemic infarcts were considered to be the sequel to the foregoing alterative and obliterative arteriolar lesion.

On gross examination, the kidneys were normal in shape, although considerably enlarged. The capsules stripped with difficulty. The surface and cut surface

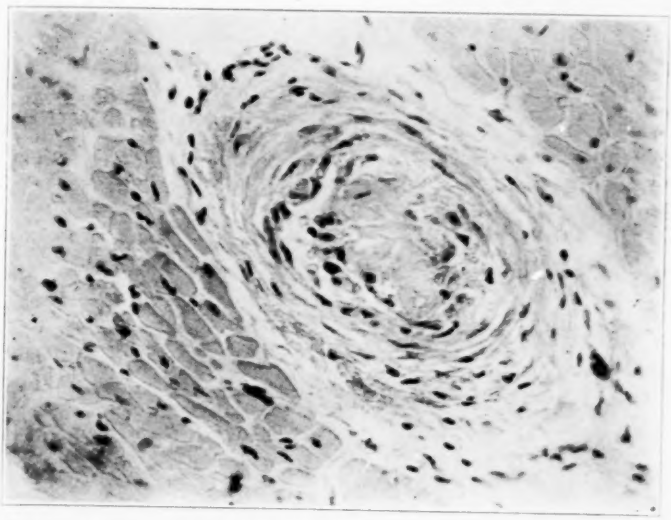

Fig. 3.—Alterative arteriolar lesion of the myocardium with homogenization of the inner layers of the vascular wall and partial obliteration of the lumen; (Leitz "Makam;" magnification, × 320).

were pale yellowish pink with innumerable, minute red dots. The normal architectural markings were distinct and the cortex relatively wide.

Microscopic sections of the kidney showed chronic degenerative changes of the corticular tubular epithelium. Hyaline casts were present in numerous tubules. A moderate increase in the interstitial connective tissue was apparent. Signs of a chronic glomerular lesion were practically absent. Evidences of an acute inflammatory lesion were found in many of the glomeruli such as necrosis of the glomerular tufts, breaking down of the nuclei, accumulation of polymorphonuclear leukocytes. While the arteries appeared normal, most of the arterioles showed lesions that were closely analogous to those of the myocardial arterioles. Homogenization and necrobiosis of the inner layers of the vascular wall were frequently seen (figs. 4 and 5). In many arterioles, proliferative endarteritic processes were pronounced and led to a more or less complete obliteration of the vascular lumen.

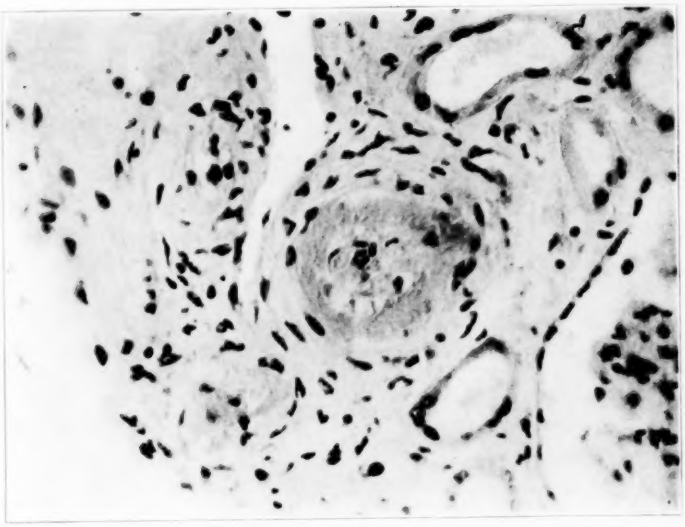

Fig. 4.—Alterative arteriolar lesion of the kidney. Note the ringlike homogeneization of the inner layers of the vascular wall and the obliteration of the lumen; (Leitz "Makam;" magnification × 320).

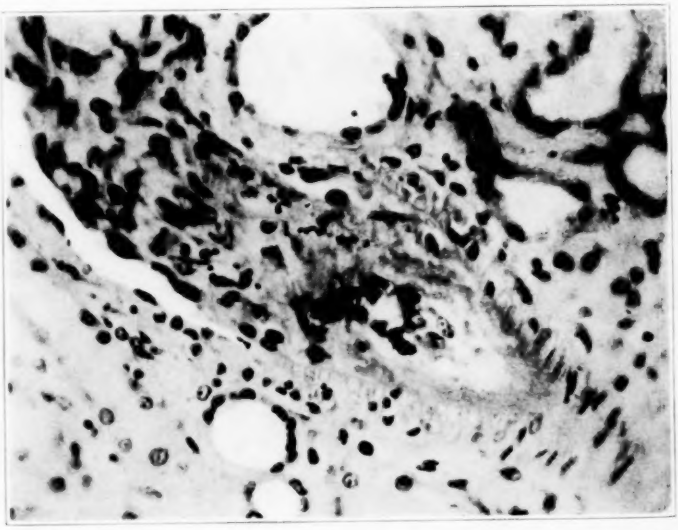

Fig. 5.—Arteriolar lesion of the kidney with homogeneization and necrobiosis of the intima, and subendothelial large cellular proliferation; (Leitz "Makam;" magnification, × 320).

The other postmortem observations that were of interest included ascites, extensive obliteration of the pericardial and pleural cavities by firm adhesions that were fibrinous in the pericardium but fibrous in the pleural cavities. There was moderate pulmonary edema. Early arteriosclerotic changes were noticed in the aorta. The spleen was moderately enlarged and firm. Chronic passive congestion of the liver and a striking intramural edema of the gallbladder were present. A culture of the blood of the heart taken at autopsy grew *Streptococcus viridans*, thus confirming the previous cultures.

COMMENT

From the anatomic point of view, the present case of sepsis due to *Streptococcus viridans* with rheumatic carditis is unusual. The pathologic observations in this case deviate from those found in the majority of such cases as both the myocardium and kidney show an alterative, productive and frequently obliterative arteriolitis. In the muscle of the heart, this arteriolar lesion resulted in the formation of areas of anemic necrosis. Alterative arteriolitis of the myocardium with subsequent necrosis of the vascular wall was referred to by Fahr [3] as an occasional observation in "rheumatic disease." The infiltration of the vascular wall with fibrin, and the appearance of homogeneous masses and subsequent necrosis are the outstanding features of the "specific" lesion of the peripheral blood vessels described by von Glahn and Pappenheim [4] in cases of rheumatic carditis. Although these authors found the typical vascular lesions in but ten of forty-seven cases, they regard them as specific, because, in their experience, the lesions are not found in any other disease. Even if the latter contention holds true, the nature of the vascular lesions cannot be wholly understood by regarding them as specific, because they are found only in the minority of the cases.

Siegmund,[5] writing about the vascular lesions in chronic streptococcic sepsis (*Streptococcus viridans* sepsis), mentioned the occurrence of alterative arterial changes with necrosis of the wall of the vessel especially in the brain and kidneys. He was impressed by the close analogy existing between these lesions and the essential features of periarteritis nodosa. Not finding the changes in the majority of cases, he did not look on them as specific. Siegmund stated that similar vascular lesions may be induced in highly sensitized animals. He was, therefore, led to the conclusion that, in his cases of chronic streptococcic sepsis, alterative vascular lesions are the manifestation of a certain "state of immunity" which he designates as "hyperergic."

3. Fahr, T.: Arch. f. Dermat. u. Syph. **130**:1, 1921.
4. von Glahn, W. C., and Pappenheim, A. M.: Am. J. Path. **2**:235, 1926.
5. Siegmund, W.: Centralbl. f. allg. Path. u. path. Anat. **35**:276, 1924.

Close morphologic analogies exist between periarteritis nodosa and the vascular lesions in the foregoing case of streptococcic sepsis. A recently observed case of periarteritis nodosa [6] gave us occasion to compare those lesions with the vascular lesions that were described in the present case. In a number of instances, it was found that the early stages of periarteritis nodosa were not distinguishable from the lesions illustrated in figure 5. A further analogy between the process under consideration and periarteritis nodosa may be found in the relationship of invading micro-organism to the host. Low virulence of the invading organism is suggested by the course of the present case and, in the opinion of competent observers, it is likewise an essential etiologic factor for periarteritis nodosa (Gruber [7]).

Evidence of the lack of specificity of this vascular lesion is also afforded by a recent case of chronic sepsis with a postmortem blood culture of *Streptococcus hemolyticus*. This patient gave no clinical or anatomic evidences of rheumatic disease, but did show vascular lesions of the kidney which were identical with those in the case now under discussion.

In view of the reported occurrence of this arteriolar lesion by others and of our own experience with it in cases of periarteritis nodosa and infection due to *Streptococcus hemolyticus*, the alterative arteriolitis which was found in the present case cannot be looked on as a specific lesion of rheumatic carditis. It appears rather that a relationship may exist between the development of vascular lesions of the type described and the degree of adaptation of the invading micro-organism to the host.

The clinical aspects of the case tend to support this conception of the relationship of organism to host. The fundamental disease was undoubtedly streptococcic sepsis, but of an intensity insufficient to elicit the usual signs of body reaction. The past history gives no clearcut story of previous streptococcic invasions. At the time of admission, an acute condition of the throat was noted although it was quite symptomless. It is worthy of emphasis that an insidious process of such magnitude could develop without a single warning symptom prior to a few days before death. Even an anemia of 2,500,000 cells with 50 per cent hemoglobin did not reduce the actual transportation of oxygen enough to produce symptoms. Again the absence of significant fever and leukocytosis in the presence of a positive blood culture of *Streptococcus viridans* is noteworthy.

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6. Semsroth, K., and Koch, R.: Krankheitsforschung **8**:191, 1930.
7. Gruber, G. B.: Virchows Arch. f. path. Anat. **258**:441, 1925.

Anatomically, the characteristic lesion of the disease occurred in the endothelial and subendothelial structures of the valves of the heart and small arteries of the myocardium and kidneys. The endocardium and the myocardium were grossly damaged. Although one may infer from the apparent activity of the disease process that much of the anatomic change developed in six weeks, it seems probable that the heart had been seriously injured for a much longer period. The electrocardiogram that was taken a week before death showed little in contrast to the advanced pathologic changes. Low potentials in leads I and II were the outstanding phenomena. The characteristic alteration of the R-S-T interval which is frequently associated with the localized myocardial degenerations of coronary disease was not found. This observation seems significant in view of the numerous areas of infarction that were apparently due to obstruction of the local blood supply. The observed physical signs were characteristic of an active disease of the rheumatic type involving the endocardium, myocardium and pericardium, but no features were noted that were diagnostic of the type of process that was present.

Likewise in the kidney, extreme vascular damage seemed to be the basis of the degeneration. Here again, however, no basis was found for the prediction of the type of anatomic change from any of the available methods of clinical examination. The older anatomic changes were chiefly tubular and glomerular. Nephrosclerosis was conspicuously absent. These observations were scarcely to have been expected from the marked elevation of the nonprotein nitrogen and creatinine, the absence of edema, the fixed Mosenthal reaction and the negative phenolsulphonphthalein reactions. These tests properly reflected the advanced degree of injury which the kidneys had sustained, but afforded no aid in the identification of the type of process responsible for the damage.

The clinical course in the later stages of the disease seemed to depend on the relative magnitude of involvement of the vessels of the different organs. Until within a few days of his death, the circulatory apparatus as a whole was functionally adequate. Likewise the kidneys had adequately handled the essential waste products of an unrestricted life and diet for an undetermined period. In this young man with both heart and kidneys structurally badly damaged, the functional renal insufficiency proved too great, and he died of uremia. In fact, it is probable that if he had been seen for the first time in the thirty-six hours before his death, an unhesitating diagnosis of "chronic interstitial nephritis in the terminal stage" would have been made.

The point of view is therefore advanced that this case, on the basis of the anatomic and clinical evidence, was fundamentally one of low

grade sepsis in which the principal tissue reaction of the host is this unusual vascular lesion. The low virulence of the organism may be assumed to have permitted the development of the process for a prolonged period without the production of a typical host-tissue reaction to infection. The inevitable but latent symptomatology was therefore referred to the vital organs which failed secondarily to their local circulatory impairment. Such a process might be contrasted with "subacute bacterial endocarditis" which is also a streptococcic invasion, but with typical septic manifestations. In this disease the brevity of the course might preclude the development of the characteristic vascular lesions that were found in this case and, more especially, the secondary degeneration of the vital organs.

SUMMARY

An unusual case of sepsis due to *Streptococcus viridans*, with chronic and acute pancarditis and chronic and subacute nephritis is described.

A characteristic lesion that was found in the arterioles of both heart and kidneys is described at length. This lesion is regarded as causal to the secondary degeneration of both heart and kidneys.

The possible relationship of anatomic lesions and clinical course in a case of this type to low virulence of the invading organism and the absence of acute reaction on the part of the host is discussed and contrasted with more fulminating processes.

THE CLOSED INTESTINAL LOOP

II. OBSERVATIONS ON DOGS WITH JEJUNAL AND ILEAL LOOPS AND CHEMICAL ANALYSES OF THE BLOOD *

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In a preceding paper [1] a method for making an accessible closed loop in the small intestine was reported. Observations were made on the relation of hydraulic pressure in loops of jejunum to the clinical condition of the animal. The prevention of intraloop pressure by aspiration of the fluid at intervals resulted in an uneventful recovery of the animal. Distention of the loop without aspiration brought about embarrassed circulation, followed by necrosis, rupture and death.

The present report is a continuation of that work, including the making of loops in the ileum and a chemical analysis of the blood under the various clinical conditions that arose in this experimental procedure. Dogs were used throughout the experiments.

EXPERIMENTAL PROCEDURE

After entering the peritoneal cavity through a right rectus incision, a segment of ileum (or jejunum) was isolated with a suitable blood supply for making a loop from 10 to 12 cm. long. The jejunal loop was approximately 14 inches (32.53 cm.), and the ileal loop, 36 inches (91.44 cm.), below the ligament of Treitz. The ends were inverted and the continuity of the intestine reestablished by an aseptic, end-to-end anastomosis. The midline fatty appendage was then dissected back over the midline between the xiphoid process and the umbilicus, where the loop was attached by its antimesenteric border over a distance of 5 or 6 cm. with a fine silk suture which did not penetrate the submucosa. The loop thus lay between the incision and midline, with its level of attachment marked by a stitch

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* From the Department of Physiology, University of Oregon Medical School.

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1. Burget, G. E.; Martzloff, K. H.; Suckow, G. R., and Thornton, R. C. B.: The Closed Intestinal Loop: I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal, Arch. Surg. **21**:829 (Nov.) 1930.

in the skin for convenience in locating it for tapping. Further details of this procedure will be found reported elsewhere.[2]

Forty-two animals were operated on as described. Eighteen of these died within the first two weeks from the following causes: two, pneumonia; three, snuffles; one, hernia, and twelve, peritonitis. In the last group, loops of the duodenum were attempted in four animals; because of the parallel circulation with the intestine at this level, it seemed impossible to make a loop here which would be adequately nourished. The remaining twenty-four, fifteen of which had ileal and nine jejunal loops, lived in good condition for several weeks or months, and were serviceable animals in the laboratory.

All animals were given water forty-eight hours after operation and food after ninety-six hours. The temperatures were taken twice daily, and frequent observations made of the general condition during the

TABLE 1.—*Pressure Developed in Closed Loops of Ileum*

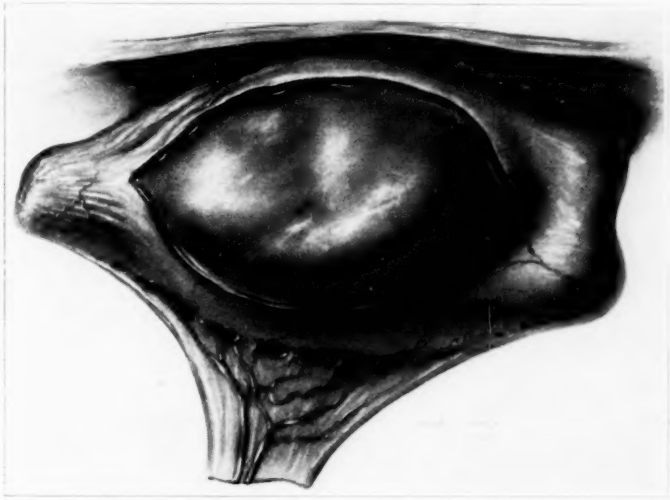
Dog	Pressure, Cm. of Water	Quantity of Fluid Withdrawn, Cc.	Days Following Operation	Length of Life Following Operation
54	30	132	9	14 days
58	55	60	7	14 days; meningitis
61	58	165	14	Alive
67	43	125	9	Alive
68	42	55	4	139 days; killed
81	37	180	7	11 days
87	30	25	2	20 days
88	41	30	2	Alive

postoperative period. Little difference was seen in the clinical condition of animals with loops at different levels. The temperature seldom rose above 102 F. unless infection was present in the incision or peritonitis developed. There was usually no vomiting, except when the loop became distended or peritonitis was present. The dogs were lively and eagerly took food and water. As a routine, aspiration was done from eighteen to twenty-four hours after operation and as frequently thereafter as seemed advisable from the previous quantity of fluid withdrawn. The low loops needed aspiration less frequently than those of the jejunum, and as the loops became older, there was less tendency for the low ones to become distended with fluid. The hydraulic pressure in the loop was measured in a number of animals during the ten days following operation. Table 1 gives the highest pressures recorded in this period with the amounts of fluid withdrawn from eight ileal loops.

The average pressure in this series was 42 cm. of water; that found under similar conditions in jejunal loops was 39.5 cm.[1] These pressures

2. Martzloff, K. H., and Burget, G. E.: An Accessible Intra-Abdominal Closed Loop of Intestine Suitable for Physiologic Studies, to be published in a later issue.

are looked on as approximating a pressure that would be effective in blocking the circulation. When it is considered that these loops had recently been subjected to trauma and that increasing pressure over twenty-four or forty-eight hours had resulted in great distention with markedly stretched capillaries, it becomes plausible that this amount of pressure might be effective in materially embarrassing the circulation. A much higher pressure is required in an acute experiment on a normal segment of intestine.[3] As indicated by the increased amount of fluid found in the loops of the ileum, there was greater distention in the ileum under an equal pressure than in the jejunum. There are probably two factors involved to account for this difference. These loops are slightly



Drawing of the loop of jejunum removed from dog 33 after thirteen months, with longitudinal incision showing putty-like material with which loop was filled

longer because of the wider branching of the mesenteric vessels of the ileum, and the thinner musculature of the ileum allows it to stretch more under a given pressure.

The character of the fluid obtained at different times varies considerably. The first specimens following operation are of a dark blood color. After from eight to ten days there is no blood present, and the fluid is dark gray, with considerable sediment. If the loop becomes markedly distended, a large part of the fluid is quite clear with sediment

3. Dragstedt, C. A.; Lang, V. G., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257 (June) 1929.

only in the last portion aspirated. On the contrary, loops that have not been disturbed for months tend to fill with a gray putty-like material, a chemical analysis of which has not been made. The accompanying illustration depicts such a loop taken from dog 33 after thirteen months. The dog was in good condition when it was killed. Grossly, the loop

TABLE 2.—*Chemical Changes of the Blood in Dogs Following the Construction of a Jejunal Loop* *

	Hours After Operation											
	Normal			48			96			144		
Dog	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide
52	30.0	362	47.0	32.0	462	38.1	35.0	412	62.7	....	....	....
77	25.8	429	51.5	37.5	439	51.5	33.3	470	53.8	37.0	440	51.5
79	26.8	406	40.3	30.6	422	40.3	39.5	380	49.3	31.6	401	56.0
89	31.9	462	39.2	34.1	495	35.8	36.6	412	58.2	25.3	412	56.0
92	29.5	462	35.9	25.8	445	42.6	23.0	462	49.3	23.5	479	51.5
93	32.6	462	44.8	40.5	412	44.8	31.0	429	44.8	31.0	429	49.3
96	31.2	412	49.3	32.0	396	51.5	28.0	380	53.8	31.2	363	56.0
97	26.5	462	47.0	30.0	429	38.1	30.2	363	44.8	35.7	346	47.0

* In this and the following tables nonprotein nitrogen and sodium chloride are given in terms of milligrams per hundred cubic centimeters of blood and carbon dioxide is given in terms of alkali reserve figure.

TABLE 3.—*Chemical Changes of the Blood in Dogs Following the Construction of an Ileal Loop*

	Hours After Operation											
	Normal			48			96			144		
Dog	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide
54	35.0	495	60.0	....	471	45.9	40.0	436	65.2	38.0	429	67.2
57	39.5	371	62.7	44.1	495	57.6	47.0	371	56.7	41.0	363	50.4
58	41.0	470	67.2	39.5	380	53.8	38.5	363	50.4	41.0	445	49.9
59	30.0	437	58.8	40.3	353	55.8	46.9	371	60.0	42.6	379	....
60	36.6	462	50.4	30.7	437	43.7	36.6	412	47.0	33.3	404	49.3
61	35.7	445	40.3	37.5	356	44.8	26.8	462	45.0	24.0	471	41.9
68	31.0	412	44.8	29.4	396	42.6	44.0	363	45.9	48.4	376	45.2
84	30.0	462	55.8	45.0	447	33.6	42.6	429	47.0	39.5	419	56.7
88	36.2	380	51.5	39.5	445	44.8	33.8	445	51.5	46.9	396	54.9
91	31.9	445	49.3	39.5	462	47.0	46.9	478	44.8	35.7	445	47.0

appeared normal with an adequate circulation. A large part of this material consisted of epithelial cells and dead bacteria.

The flora found in the ileum was similar to that in the jejunum. *Bacillus coli, Bacillus welchii,* staphylococci and streptococci predominating. Although the p_H of the fluid in the loop varied between 5.8 and 8.8 this range did not seem to affect the nature of the flora. A separate report is being made on the bacteriologic observations.

That these loops function normally when kept in good condition, that is, when they are not disturbed by distention and the formation of excess fluid and are kept washed out by the injection and withdrawal of a warm physiologic solution of sodium chloride, seems convincing from many experiments on digestion carried on by the injection of

TABLE 4.—*Chemical Changes in the Blood in Two Dogs Without Operation But Given Routine Postoperative Care and Three Dogs with End-to-End Anastomosis but Without Construction of a Loop*

	Normal			Hours After Operation								
				48			96			144		
Dog	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide
Normal I.....	39.5	445	40.3	51.7	412	42.6	44.1	429	42.6	38.0	445	49.3
Normal II.....	34.1	462	44.8	30.0	429	51.5	33.3	412	40.3	29.4	462	40.3
86.....	37.5	487	47.0	31.0	511	40.3	29.4	412	38.1	....	....	....
94.....	39.5	429	42.7	35.7	429	51.5	30.6	445	44.8	39.5	396	47.0
95.....	34.9	445	49.3	35.4	462	44.8	25.4	495	40.3	31.9	429	44.8

TABLE 5.—*Chemical Changes of the Blood in Dogs with Ruptured Loops and Peritonitis*

Dog 48				Dog 50				
Date	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment	Date	Non-protein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment
10/19/29	41.9	454	51.2	Normal	11/1/29	56.0	412	51.5	Normal
19	....	...	....	Operation	2	....	...	....	Operation
20	39.5	445	51.2		4	45.0	454	47.0	Vomited
21	50.0	379	49.2		5	47.0	433	47.0	Vomited
22	52.0	412	47.0		7	55.0	330	56.0	
24	45.4	388	50.4		8	....	...	....	Dead
26	48.5	375	61.6						
28	60.5	406	53.8						
29	....	...	....	Died					
Dog 78					Dog 63				
3/17/30	33.4	429	50.8	Normal	2/1/30	46.9	406	47.0	Normal
18	....	...	....	Operation	1	....	...	....	Operation
20	37.7	429	42.5		3	50.2	379	47.0	
22	50.0	363	65.0		4	55.6	313	45.9	Vomited
23	....	...	....	Vomited	5	....	...	....	Dead
24	50.0	363	69.4						
26	46.3	330	72.8						
28	51.0	440	75.9						
4/1	37.7	280	....	Died					

substances into the loop and later by the withdrawal and washing out of the loop. The unabsorbed portion indicates indirectly how much of the injected substance has been taken up. In order to be certain on this point, many animals were killed for histologic examination of the loop. When the circulation is good and there has been no complication in the clinical recovery, microscopic examination of the mucosa reveals no changes that cannot be demonstrated in sections of normal intestine.

The use of such loops for experiments on digestion and absorption seems to us to have advantages over the other methods used.

Since the closed loop has been used by different investigators to simulate intestinal obstruction, an analysis for chemical changes in the blood has been made as a matter of routine. Eleven cubic centimeters of blood were drawn from the left ventricle of the heart before operation and every forty-eight hours thereafter until recovery. Nonprotein nitrogen was determined by the method described by Koch and McMeekin,[4] chlorides, according to Whitehorn [5] and the carbon dioxide combining power after the Haskins-Osgood modification of the Van Slyke titration method.[6] Table 2 gives the results in dogs with jejunal loops, and table 3, the results in those with low loops. In neither group is there any noteworthy change from the normal. As a further

TABLE 6.—*Chemical Changes in the Blood Following Vomiting in Dogs with Old Loops*

Dog 32					Dog 40				
Date	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment	Date	Nonprotein Nitrogen	Sodium Chloride	Carbon Dioxide	Comment
12 11 29	30.0	482	59.4	Normal	11 11 29	50.0	371	73.9	Vomited
5 20 30	24.4	421	60.5	Vomited	15	....	....	....	Vomited
7 16	28.8	393	60.5		16	62.5	330	78.4	
17	32.0	330	58.2		18	44.0	326	86.2	Vomited
					7 17 30	30.0	412	67.2	Normal
Dog 80									
6 14 30	36.6	412	58.2	Normal					
7 13	....	....	....	Vomited					
14	36.0	412	49.3						
16	46.9	315	69.4						
17	40.0	330	73.9						
18	....	....	....	Recovered					

comparison, in table 4 are given the observations in two normal dogs and in three dogs without loops in which end-to-end anastomosis had been performed. All received postoperative care as described for dogs with loops. The range of variation was as great as that in the foregoing groups. Table 5 shows the effect in four dogs with ruptured loops and peritonitis. The nonprotein nitrogen showed a moderate rise, especially on the day of death, and the chlorides fell, but not markedly. There was slight vomiting in each case expect that of dog 48. The effect of distention in an old loop to the point of repeated vomiting, but not

4. Koch, F. C., and McMeekin, T. L.: A New Direct Nesslerization Micro-Kjeldahl Method and Modification of the Nessler-Folin Reagent for Ammonia, J. Am. Chem. Soc. **46**:2066 (Sept.) 1924.

5. Whitehorn, J. C.: A System of Blood Analysis, J. Biol. Chem. **45**:449 (Feb.) 1921.

6. Haskins, H. D., and Osgood, E. E.: Modification of Van Slyke's Method for Estimating the Alkali Reserve of the Blood, J. Lab. & Clin. Med. **6**:37, 1920.

carried far enough to cause gangrenous areas with rupture, is shown for dogs 32, 49 and 89 in table 6. There was a tendency toward a rise in nonprotein nitrogen and a fall in chlorides. The lack of marked changes in the blood would indicate that the vomiting was caused reflexly by distention of the loop. This is further brought out by the fact that these animals will take food almost at once following withdrawal of the fluid in the loop.

COMMENT

These observations indicate relatively unimportant changes in the chemistry of the blood in dogs with closed loops in which pressure in the loop is not permitted to bring on necrosis. There is no marked toxemia and no vomiting. Dragstedt [7] observed that if distention is relieved by aspiration of the fluid in the loop, the toxemia is relieved, and the blood chlorides tend to return to the normal level. While our results in dogs in which the loop was allowed to become distended show a moderate fall in blood chlorides, the toxemia was not great, as indicated by the fact that the animals would eat almost immediately following aspiration of the fluid in the loop. It would seem that vomiting accounts for the decrease in chlorides in these cases. Wangensteen and Waldron [8] did not find a low level of blood chlorides in closed loops with gangrene when the continuity of the intestinal tract was reestablished. Further evidence on this point is shown in the dogs here reported with ruptured loops and peritonitis.

CONCLUSIONS

1. Dogs with closed intestinal loops (ileum and jejunum) have been kept alive for periods of from several months to more than a year by aspirating the loop and preventing overdistention.

2. After the first ten days, tapping becomes unnecessary except at infrequent intervals. The loops in the ileum are distended less frequently than those in the jejunum.

3. There is no difference in the clinical condition during recovery between animals with jejunal loops and those with loops in the ileum.

4. Closed loops in dogs that have made an uneventful recovery are normal histologically; physiologically, they digest and absorb food substances at a normal rate.

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7. Dragstedt, T. R.: Blood Chemistry in Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **25**:239, 1928.

8. Wangensteen, O. H., and Waldron, G. W.: Studies in Intestinal Obstruction: IV. Strangulation Obstruction; A Comparison of the Toxicity of the Intestine and Other Tissues Autolized in Vivo and in Vitro, Arch. Surg. **17**:430 (Sept.) 1928.

5. When absorption and secretion tend to remain balanced and the loop is not washed out, it gradually fills with a thick, gray, putty-like substance.

6. The chemistry of the blood was practically normal throughout the uncomplicated recovery of these animals. Distention of the loop accompanied by vomiting or rupture of the loop, with peritonitis and vomiting, causes some fall in the blood chlorides and a moderate rise in nonprotein nitrogen.

CLEAR FLUID TEST MEALS (WATER, CAFFEINE SOLUTION, ALCOHOL) FOR USE IN FRACTIONAL GASTRIC ANALYSIS*

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The merits of the fractional method of studying the gastric contents of the stomach have been conclusively established (Rehfuss[1]). As a routine office procedure, however, I fully agree with the recent views so aptly expressed by Kaufmann[2] that a single specimen gastric test meal, carefully obtained and studied, fully suffices or may even be advantageous for general diagnostic purposes or as an index of gastric secretion and digestion. The fractional method should not replace, but supplement, the original single specimen gastric test. If one desires a more detailed study of the degree or curve of the acid wave, then there is no doubt that the extractions made at frequent intervals elicit more exact information. Every one is aware of instances in which the single extraction test meal did not reveal free hydrochloric acid, whereas the repeated extractions made in the same patient showed acids at one period or another. The relative advantages of these two methods have been fully and ably discussed, among others, by Hurst,[3] Eggleston,[4] Friedenwald, Gantt and Morrison,[5] Friedenwald and Bryan,[6] Hubbard and Lichty[7] and Rehfuss.[8]

When the fractional method was first introduced, the Ewald-Boas test meal, which had so successfully proved its merits in the single extraction method, was automatically adopted for the fractional method.

* Submitted for publication, July 23, 1930.

* Presented in preliminary form at the meeting of the American Gastro-Enterological Association, April 30, 1928.

1. Rehfuss, M. E.: Am. J. M. Sc. **147**:848, 1914; Ann. Clin. Med. **2**:55, 1923.
2. Kaufmann, J.: Arch. f. Verdauungskr. (Boas Festschrift) **43**:230, 1928.
3. Hurst, A. F.: Lancet **1**:111, 1923.
4. Eggleston, E. L.: Gastric Secretory Disturbances, J. A. M. A. **83**:260 (July 26) 1924.
5. Friedenwald, J., Gantt, W. H., and Morrison: Ann. Clin. Med. **2**:292, 1924.
6. Friedenwald, J., and Bryan, W. J.: Presence of True Hydrochloric Acid in Gastric Contents in Carcinoma of the Stomach, J. A. M. A. **83**:265 (July 26) 1924.
7. Hubbard, R. S., and Lichty, J. A.: Ann. Clin. Med. **4**:393 (Nov.) 1925.
8. Rehfuss, M. E.: Ann. Clin. Med. **2**:55 (July) 1923.

In some of the clinics abroad, however, I have observed the routine use of clear fluid test meals. The three test meals most frequently mentioned in the literature are caffeine solution, alcohol solution and plain water. In this study I should compare these with the Ewald-Boas test meal, as few detailed comparative statistics exist.

The test meals studied were: 1. The Ewald-Boas test meal: two slices of toast and a glass (240 cc.) of weak tea. 2. The water test meal: 400 cc. of ordinary tap water at room temperature. Distilled water and water at different temperatures were tried, but no outstanding differences were noted in the resulting gastric secretion. 3. The alcohol test meal: 300 cc. of a 5 per cent pure alcohol solution. 4. The caffeine test meal: 400 cc. of the following caffeine solution: caffeine purum 0.2 and water, 400 cc. All of these clear test meals were colored a faint blue by the addition of three drops of a 2 per cent solution of aqueous methylene blue (Katsch and Kalk[9]).

TECHNIC

The usual technic for fractional test meals was employed. The Einhorn duodenal tube was passed through the mouth into the stomach as soon as the patient awoke in the morning, any gastric contents possibly remaining in the fasting stomach were aspirated, and the respective test meal was given either by mouth or directly through the tube. Every fifteen minutes thereafter a 10 cc. sample was aspirated; aspiration was repeated as long as the gastric contents persisted. The methylene blue (methylthionine chloride, U. S. P.) stain was employed to indicate when the test meal had left the stomach. The contents gradually became a fainter blue the later they were aspirated, until finally a colorless liquid indicated that the test meal had entirely left the stomach. The subsequent contents aspirated were mainly of pure gastric secretion; aspiration was continued until no more secretion could be obtained. In this way some idea was gained as to the rapidity with which the contents left the stomach and the type of secretion remaining in the stomach after the test meal. Regurgitating bile or duodenal contents were at once evidenced by the change of the methylene blue to an easily recognizable, characteristic greenish hue.

MATERIAL FOR STUDY

Patients were selected from the general medical ward of the Lenox Hill Hospital and included persons with normal digestions as well as those with functional and organic lesions of the digestive tract.

On three successive days plain water, caffeine and Ewald test meals, were given to forty patients and the results were studied, respectively. An alcohol test meal was given on the fourth day to fifteen of the patients. The results of the plain water test meal given alone on three successive days were studied in three cases. Similar repeated experiments were made in three patients with the caffeine test meal alone, in three patients with the alcohol test meal alone and in three patients with the Ewald-Boas meal.

9. Katsch, G., and Kalk, H.: Klin. Wchnschr. **4**:2190 (Nov. 12) 1925.

RESULTS

Space does not permit the detailed publication of all the figures or charts obtained in these experiments, but a general analysis is given in the accompanying table.

In 65 per cent (twenty-six cases) the four test meals gave almost identical results; i.e., the determinations for the free and total acids varied only within ten points (chart 1). In 35 per cent (fourteen cases) there were variations in the degree of acidity as high as twenty-five points; there was, however, no uniformity in these differences. Thus, of these patients, six (43 per cent) manifested the highest figures for acid secretion after the alcohol test meal; three (20 per cent), after the caffeine meal and two (14 per cent), following the Ewald test

Analysis of Forty Cases Studied by the Fractional Method, with the Ewald, Water, Caffeine and Alcohol Test Meals

	Number of Cases	Per Cent	Acid Figure	Free Hydrochloric Acid	Total Acidity
Same results	16	62	High	From 50 to 80	From 80 to 110
	4	16	Normal	From 20 to 50	From 40 to 70
	3	11	Low	Below 20	Below 40
	3	11	Achylia		
Total.....	26	65			
Different results	3	20	High		
	4	29	Normal		
	5	35	Low		
	2	14	Achylia		
Total.....	14	35			
Highest figures	6	43	After alcohol meal		
	3	21	After caffeine meal		
	2	15	After Ewald meal		
	3	21	After water meal		

meal, while in three (20 per cent) the water meal appeared to be the most stimulating. It can therefore readily be seen that all types of differences were noted; but in general the alcohol meal was the most stimulating to secretion, while the other meals gave practically the same results.

The lack of agreement between the secretion stimulated by the various test meals was noted mainly in patients with gastric secretions of normal or lowered acid figures. In cases with high figures for acidity or complete anacidity the results were more uniform. Thus, in a group of twenty-six cases in which the determinations were the same, sixteen showed high figures for acidity (free hydrochloric acid from 50 to 80, total acid from 100 to 110); four, normal acidity (free hydrochloric acid from 20 to 50, total acid from 40 to 70); three, subacidity (free hydrochloric acid below 20, total acid 40 or less), and three, achylia. Of the fourteen cases in which there were varying

results, three showed high figures for acidity; four, normal acidity; five subacidity, and two, achylia.

The only outstanding discrepancy in the results of the tests occurred in two cases in which the fractional water test meal did not stimulate free hydrochloric acid on two and three different days, respectively, while the other test meals gave normal acid figures.

When control experiments were performed in which patients received the same type of test meal on three successive days, just as many and as striking differences were noted in the degree of acidity on the

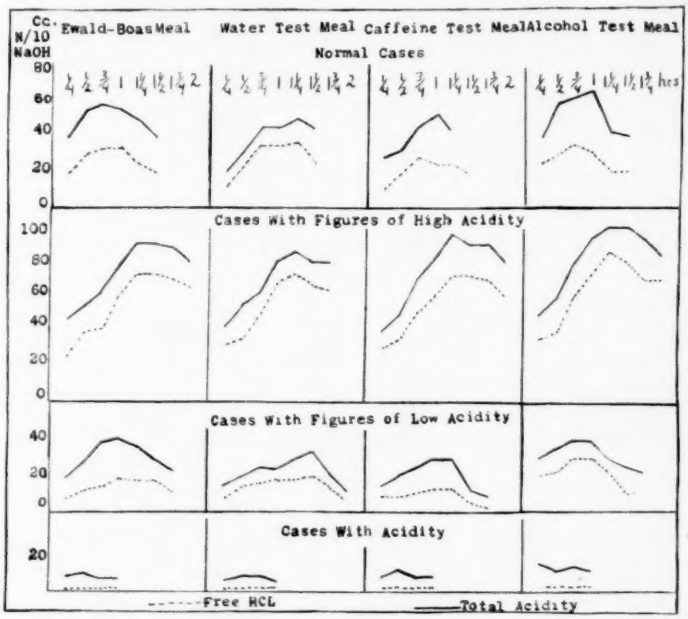

Chart 1.—Comparative determinations after different types of test meals in which the results were practically the same.

different days, after the same type of meal, irrespective of whether the meal was of tea and toast, water, caffeine or alcohol, as were evidenced after the different test meals (chart 2). This proved that the nature of the test meal was not the sole cause for the variability in the results. It was found that duodenal regurgitation was a frequent factor in the variations both when different test meals were used and when the same type of meal was repeated. The clear fluid test meals demonstrated this fact conclusively, as in these instances the slightest amount of regurgitated bile and the consequent immediate

lowering of the gastric acidity were at once noted. This diminished acidity might occur only in the contents of one extraction, the following specimen, extracted in fifteen minutes, showing normal acidity, or the regurgitation might persist and give a lowered acidity over a longer period of time. The blue color of the test meal would assume a characteristic greenish hue as soon as any form of alkaline duodenal con-

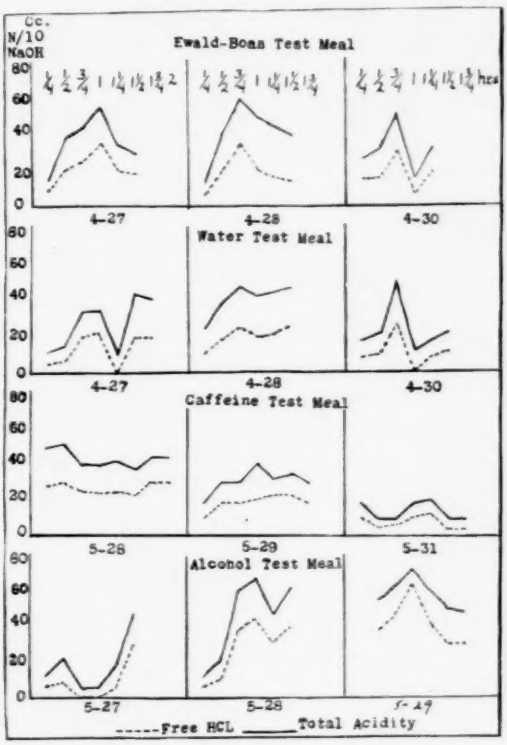

Chart 2.—The same type of test meal repeated on successive days with striking differences in the results.

tents would flow back into the stomach. The clear fluid test meals, which were uncolored by methylene blue, would show that regurgitation took place only if greenish or yellowish bile would regurgitate, but not if unpigmented intestinal contents would flow back. When one realizes that the intestinal contents are at least five times as alkaline as bile, the importance of the element of intestinal regurgitation becomes evident. It is more difficult to detect regurgitation with the Ewald meal, even

though stained with methylene blue, because of the brown color of the tea and toast, which interferes with the macroscopic detection by the change of color.

Gaither[10] too, has shown that one spurt of golden yellow bile may reduce the gastric acidity for a period of from ten to thirty minutes. Whether the reduction of acid is due to its neutralization by the intestinal contents or to true inhibition of the activity of the gastric glands is impossible to state. Macroscopic regurgitation occurred in our experiments in 7 per cent of the tests with the Ewald meal; in 11 per cent, with the caffeine meal; in 19 per cent, with the alcohol meal, and in 18 per cent, with the water meal.

While these figures show that regurgitation occurs twice as often with clear fluid meals as it does with the Ewald meal, it is possible that this greater frequency is apparent only because of the aforementioned difficulty in recognizing regurgitation with the tea and toast. This is particularly true if the regurgitation is slight and the consequent reduction of acidity results not in complete anacidity, but in a lowering of the acid figures.

WATER TEST MEAL

In the earliest studies of the gastric contents, von Leube (cited by Kaufmann [2]) employed water in the stimulation of gastric secretion. He used ice water and intended the coldness to be a factor in the stimulation of the acids. Water is well known to be a gastric stimulant (Heidenhain,[11] Sanotski,[12] Pavlov,[13] Foster and Lambert,[14] Bergeim, Rehfuss and Hawk,[15] Sawitch and Zeliony,[16] Carlson, Orr and Brinkman [17]). Bergeim, Rehfuss and Hawk [15] applied this knowledge practically in the form of a test meal consisting of 400 cc. of water, and reported almost exactly the same acid curve with this test as with the Ewald meal. They felt that in the average normal person, water, either cold or warm, produced as great a stimulation as does the Ewald meal and can be substituted for it. Ivy [18] also showed that 400 cc. of water could be used for the determination of acids in the stomach.

10. Gaither, E. H.: Effects of Surgery of Stomach on its Subsequent Motor and Secretory Function, J. A. M. A. **91**:1079 (Oct. 13) 1928.

11. Heidenhain: Arch. f. d. ges. Physiol. **19**:148, 1877.

12. Sanotski: Arch. di sc. biol. **1**:589, 1892.

13. Pavlov, I. P.: The Work of Digestive Glands (trans. by Thompson) ed. 2, London, C. Griffin & Company, 1910.

14. Foster and Lambert: J. Exper. Med. **10**:820, 1908.

15. Bergeim, O.; Rehfuss, M. E., and Hawk, P. B.: J. Biol. Chem. **29**:345, 1914.

16. Sawitch and Zeliony: Arch. f. d. ges. Physiol. **110**:123, 1913.

17. Carlson; Orr, and Brinkman: Am. J. Physiol. **33**:91, 1914.

18. Ivy, A. C.: Am. J. Physiol. **46**:420 (July) 1918.

but he did not feel that it could be substituted for the Ewald meal, as there is a marked variation in the response to stimulation by water in different persons. He met with several instances, as I have, in which secretion in the stomach was not stimulated by the ingestion of water. The stomachs that empty water slowly (150 cc. or less in fifteen minutes) respond much more readily than those that empty water quickly. Moffatt, Mitchell and Powell [19] found that some subjects show a complete achylia with water test meals, who give an acid curve of average height with a gruel meal. They objected to the water meal because of the difficulty in estimating the precise rate of emptying the stomach. This objection can be overcome, as I have shown, by the use of methylene blue.

The mechanism whereby water acts as a stimulant is not entirely agreed on and may, therefore, be due not to one but to several factors. Pavlov [13] thought that the stimulation is chemical and due to the "prolonged and widespread contact" of the water with the gastric mucosa. This seems to be corroborated by the work of Foster and Lambert,[14] who showed that the flow of gastric juice following the introduction of water is directly proportional to the volume of water employed, and by the work of Ivy,[18] who found that the stomachs that are emptied of water slowly respond much more actively than those that are emptied quickly. He also noted a latent period of seven minutes for the human gastric glands when they were stimulated by water. Bergeim, Rehfuss and Hawk,[15] however, were not able to demonstrate any latent period, and thus felt that a prolonged and widespread contact with the mucosa of the stomach was not necessarily a preliminary to stimulation in the human being, as Pavlov claimed to be necessary in dogs. Carlson, Orr and Brinkman [17] suggested that "water washed traces of gastric secretogogues into the intestines where they are absorbed and act on the gastric glands via the blood." It was also thought possible that the stimulating power of ordinary water was due to electrolytes contained in it, but comparative tests made with distilled water did not show striking or consistent differences; in fact, in one case, higher acid figures were obtained with the distilled water than with the tap water.

ALCOHOL TEST MEAL

The action of alcohol in various dilutions on the mucous membrane of the stomach has received a great deal of attention in the literature. The article by Kast [20] gives a splendid complete survey of the subject.

19. Moffatt, P. McG; Mitchell, G. O., and Powell, A. T. W.: Guy's Hosp. Rep. **71**:1, 1921.

20. Kast, L.: Arch. f. Verdauungskr. **12**:486, 1906.

Kast (also quoted by Kelling [21]) showed that a solution of alcohol of less than 10 per cent is an excitant to gastric acids but not a stimulant to the superficial mucous membrane. It was not, however, until 1914 that Ehrmann [22] suggested a 5 per cent alcohol solution as a gastric test meal (10 cc. of absolute alcohol in 200 cc. of water). He advised its use because it made a complete homogeneous solution, had no sediment or albumin, was sterile, could be easily sterilized for the study of gastric bacteria, was a strong gastric stimulant even when the patient had no appetite and could be extracted from the stomach through a small gastric tube. He employed it in the single extraction method and from one half to three quarters of an hour after its ingestion, he was able to extract contents of almost pure gastric secretion.

Da Silva Mello [23] used an alcohol meal in the single extraction method (300 cc. of a 5 per cent alcohol solution) in twenty-five patients. The acids were readily estimated, but he noted a regurgitation of bile in 90 per cent of the cases. As early as 1886, Gluzinski [24] had used a solution of alcohol of from 25 to 50 per cent for the express purpose of getting a reflow of bile into the stomach. The regurgitation of bile and duodenal contents was noted also by others (von Soos [25] and San Philippo [26] and became the outstanding objection to the use of the alcohol meal on account of the neutralization of the acids by the strongly alkaline duodenal contents. Grote [27] found that the alcohol meals gave figures for acidity that were about one-third lower than the degree of acidity after the Ewald-Boas test meals. Von Friedrich and Neumann [28] found regurgitation in 25 per cent of cases. Kotscham [29] found anacidity in thirty-three of seventy-two cases.

On the other hand, Kelling,[30] Wönckhaus [31] and Vandorfy and Várady-Borbély [32] employed the alcohol meal for the fractional analysis method, and were favorably impressed with its results. The latter

21. Kelling: Arch. f. Verdauungskr. **12**:491, 1906.

22. Ehrmann: Berl. klin. Wchnschr. **51**:662, 1914.

23. da Silva Mello: Berl. klin. Wchnschr. **53**:275, 1926.

24. Gluzinski: Deutsches Arch. f. klin. Med. **39**:405, 1886.

25. von Soos: Orvosi hetil., 1917, vol. 61, no. 1.

26. San Philippo: Zentralbl. f. inn. Med. **42**:382, 1921.

27. Grote: Stomach Functional Test, Klin. Wchnschr. **3**:792 (April 29) 1924.

28. von Friedrich, L., and Neumann, K. E.: Deutsche med. Wchnschr. **47**:43 (Jan. 13) 1921.

29. Kotscham: Cited in Klin. Wchnschr., July 16, 1925.

30. Kelling: Arch. f. Verdauungskr. **24**:1, 1918.

31. Wönckhaus: Deutsche med. Wchnschr. **47**:43 (Jan. 13) 1921.

32. Vandorfy and Várady-Borbély: Ztschr. f. d. ges. exper. Med. **50**:615, 1926.

studied twenty-five patients in whom comparative tests with the plain water meal were made with practically identical results. In cases with high figures for acidity the water gave as good results as did the alcohol test meal. In cases of duodenal ulcer the water meal gave even higher figures. In cases with normal or subnormal figures for acidity, the water stimulation gave lower results than did the alcohol meal.

There seems to be no doubt that regurgitation is apparent less often with the Ewald meal than with the clear meals, and apparent more often with the alcohol than with the water meal. Because it is more readily recognized with the clear than with the Ewald meal, it can at once be considered as an explanation for a particularly low or absent acid secretion.

CAFFEINE TEST MEAL

Katsch and Kalk [9] were the first to advise the use of a caffeine test meal. After trying various preparations and dilutions, they finally employed 0.2 Gm. of caffeine purum in 300 cc. of water. They realized the advantages of a clear fluid test meal free from albumin and salts, particularly in certain forms of examinations, but considered alcohol too irritating and nonphysiologic in its action. They compared the results in twenty-five patients tested with the alcohol and caffeine meals by the single extraction method and found the stimulating action of alcohol greater than that of caffeine. In two cases of borderline acid production, however, alcohol gave no secretion of free acid while caffeine did. They felt that the secretion following caffeine was not due to the direct irritation of the gastric mucosa, but to the stimulation of the acid-forming elements of the blood. A caffeine solution must not be confused with a solution of coffee, as the latter contains the additional products of roasting, among them probably histamine. Pincussohn,[33] however, showed that in dogs the caffeine solution produced no greater results than did the water in which the caffeine was dissolved. Goldbloom [34] too, inserted first a caffeine solution and then water into the large stomach of a dog with a Pavlov stomach, and watched the secretion in the small stomach. He found no difference between the caffeine and the water as far as the resulting secretions were concerned. Goldbloom carried out comparative tests with caffeine, water and alcohol by the single extraction method, and found that in 50 per cent of cases the caffeine gave little or no secretion after twenty or twenty-five minutes, while water showed secretion in 80 per cent of the cases and alcohol in almost 100 per cent.

33. Pincussohn, L.: Ztschr. f. Phys. u. diätet. Therap. **11**:261, 1907.

34. Goldbloom, A. A.: Arch. f. Verdauungskr. **42**:13 (Feb.) 1928.

COMMENT AND CONCLUSIONS

The Ewald-Boas tea and toast breakfast is undoubtedly the most practical test meal for the routine single extraction gastric analysis. Clear fluid test meals used in the single extraction method have as their great disadvantage the fact that they leave the stomach too rapidly, and that very often the stomach is empty after forty-five minutes. They can, however, be employed with advantage (Cheney[35]) when one is especially desirous of studying the gastric cellular elements or food remnants, because they make a complete homogeneous solution and give no sediment. Furthermore, these clear test meals are free from albumin and salts, which is an essential in certain gastric tests, and in the study of bacteria they can be rendered sterile more readily. When the repeated extraction method of gastric analysis is employed instead of the single extraction method, these advantages of the clear fluid test meal hold true to even a greater extent. In addition, a gastric content of clear fluid can be extracted through the small duodenal tube more easily than can that of tea and toast, and the subsequent titration for the acids can be carried out without previous filtration of the numerous samples. The often quoted disadvantage of the clear fluid meals is that duodenal regurgitation occurs more often with them than with the Ewald meal; this, however, may be more apparent than real, and even if it does occur more frequently, it is readily recognized macroscopically and can be immediately taken into consideration. With the Ewald meal there is a risk that slight or moderate regurgitation may be entirely overlooked.

The clear fluid meals that have been employed are of plain water, an alcohol solution and a caffeine solution. The secretions following their ingestion have been compared with those after the meal of tea and toast. In 65 per cent of the cases the results of these three test meals are practically the same, so that any one can be employed in a fractional gastric analysis instead of the Ewald-Boas meal (chart 1). The differing results in the remaining 35 per cent of the cases need not necessarily be explained on the basis of the different constituents of the test meals; they can as well be attributed to the variations occurring in aliquot fractions obtained during a single analysis, and to the individual variations in a patient from day to day. The former factor has been definitely shown by the work of Kopeloff,[36] while the latter has been proved by myself in the series of experiments in which repeated examinations on three successive days showed widely varying results with the same type of test meal (chart 2).

35. Cheney, W. F.: Tr. Am. Gastro-Enterol. A. 1928, p. 55.

36. Kopeloff, Nicholas: Proc. Soc. Exper. Biol. & Med. **19**:154, 1922; Variations in Aliquot Fractions of Gastric Contents, Arch. Int. Med. **30**:118 (July) 1922.

Of these clear fluid meals, alcohol is the most stimulating to gastric secretion; it is more stimulating than the Ewald-Boas meal. It has the disadvantage of producing in many patients, particularly in women who are unaccustomed to alcoholic drink, transient intoxicating effects. The scarcity of good alcohol in this country of prohibition is also a disadvantage.

The water meal is undoubtedly the simplest; it can be used any place or any time without preparation. It compares favorably with the other meals; in fact, the stimulating effect of the caffeine meal or the Ewald test meal may be due to the water element, as water is undoubtedly a strong gastric stimulant. However, there are occasional persons who do not secrete free hydrochloric acid in response to water, so that anacidity following a water meal must be controlled by an Ewald-Boas meal or by the use of histamine. The latter precaution has been adopted recently by many authorities when anacidity is found to follow any type of test meal.

EXPERIMENTAL AND CLINICAL STUDIES OF ERGOTAMINE

IV. THE EFFECT OF ERGOTAMINE ON THE BASAL METABOLISM, CIRCULATION AND BLOOD SUGAR OF NORMAL PERSONS AND OF PATIENTS WITH THYROTOXICOSIS *

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AND
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Ergotamine and the closely related and pharmacologically similar ergotoxin constitute the principal alkaloids of ergot and exhibit all the effects of that drug on the uterus. In addition they have been shown to exert an effect on various parts of the sympathetic nervous system, in particular, a paralyzing or depressing action on the motor elements of that system that are stimulated by epinephrine. Briefly, in animals they not only antagonize the pressor effect of epinephrine on the systemic arteries, but under suitable conditions cause a reversal of the usual effect of epinephrine on the blood pressure.[1] Ergotamine inhibits the dilator effect of epinephrine on the coronaries,[2] and by its effect on the sympathetic nerves of the heart is said to slow the rate of sinus rhythm [3] and to neutralize the accelerator action of epinephrine.[4] In addition, ergotamine has been reported both to lower [5] and to raise [6] the blood

* Submitted for publication, Aug. 16, 1930.

* From the Department of Medicine, Vanderbilt University School of Medicine.

1. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. **34**:163, 1906.

2. Rothlin, E.: Ueber die pharmakologische und therapeutische Wirkung des Ergotamins auf den Sympathicus, Klin. Wchnschr. **4**:1437, 1925.

3. Andrus, E. C., and Martin, L. E.: The Action of the Sympathetic upon the Excitatory Process in the Mammalian Heart, J. Exper. Med. **95**:1017, 1927.

4. Kolm, R., and Pick, E. P.: Ueber die Bedeutung des Calciums für die Erregbarkeit der sympathischen Herznervenendigungen, Arch. f. d. ges. Physiol. **189**:137, 1921.

5. Lesser, E. J., and Zipf, K.: Ueber Herabsetzung des Blutzuckers beim normalen Kaninchen durch Ergotamin, Biochem. Ztschr. **140**:612, 1923. Seidel, W.: Die Wirkung des Ergotamins (Gynergen) auf den Blutzuckerspiegel beim Kaninchen und beim Menschen, Arch. f. exper. Path. u. Pharmakol. **125**:269, 1927.

6. Farrar, G. C., Jr., and Duff, A. M., Jr.: Ergotamine Tartrate: Its Direct Hyperglycemic Action and Its Influence on the Hyperglycemia Produced by Epinephrine in Normal Unanesthetized Dogs, J. Pharmacol. & Exper. Therap. **34**:197, 1928.

sugar level during fasting, to diminish the hyperglycemic response to epinephrine [7] and to lower the production of heat.[8] Certain writers, notably Rothlin,[9] maintain that ergotamine also possesses a similar paralyzing action on certain of the inhibitory elements of the sympathetic system and is able, for example, to annul the inhibitory action of epinephrine on the small intestine. A more complete review of the literature dealing with experiments on animals is found in our previous publications.[10]

Because of these actions on the sympathetic system, ergotamine has become of considerable interest outside the field of obstetrics and has been used rather extensively in animal and clinical experiments in attempts to obtain direct or indirect evidence respecting the functions and behavior of the sympathetic nervous system. More recently it has been recommended as a therapeutic agent in conditions in which an overactivity of the sympathetic system exists, or is thought to exist, notably in cases of thyrotoxicosis.

However, as we have stated in preceding papers, the use of ergotamine for these purposes is based on evidence obtained for the most part from experiments on animals in which the doses employed and the conditions of the experiments were not such as are applicable to human subjects. Many of the clinical experiments purporting to show an action of ergotamine in man similar to that in animals have been poorly controlled. In other experiments it has simply been assumed that the action was the same. In view of these facts it was thought advisable, before carrying out certain projected experiments dealing with some of the functions of the sympathetic nervous system, to investigate certain effects of the drug. This has been done, trained normal dogs and normal persons being used as subjects, and the effect of ergotamine on the blood sugar, circulation and basal metabolism has been studied. Our

7. Michulicich, M.: Ueber Glykosuriehemmung: II. Ueber den Einfluss von Ergotoxin auf die Adrenalin und Diuretinglykosurie, Arch. f. exper. Path. u. Pharmakol. **69**:133, 1912. Rothlin, E.: Zur Pharmakologie des Blutzuckers, Rev. de pharmacol. et de therap. exper. **1**:103 (Sept.) 1928.

8. Marine, D.; Deutch, M., and Cipra, A.: Effect of Ergotamine Tartrate on the Heat Production of Normal and Thyroidectomized Rabbits, Proc. Soc. Exper. Biol. & Med. **24**:662, 1927.

9. Rothlin, E.: The Specific Action of Ergot Alkaloids on the Sympathetic Nervous System, J. Pharmacol. & Exper. Therap. **36**:657 (Aug.) 1929.

10. Youmans, J. B., and Trimble, W. H.: Experimental and Clinical Studies of Ergotamine: I. Effect of Ergotamine on the Blood Sugar and Epinephrine Hyperglycemia in Trained, Unanesthetized Dogs, J. Pharmacol. & Exper. Therap. **38**:121, 1930; II. The Effect of Ergotamine on the Heart Rate of Trained, Unanesthetized Dogs, ibid. **38**:133, 1930; III. The Effect of Ergotamine on the Oxygen Consumption of Normal Trained Dogs, ibid. **39**:201, 1930.

experiments on animals [3] which have been reported elsewhere,[10] have shown under these conditions results that have differed in some respects from those previously described. The present paper deals with the results obtained with normal human subjects together with observations made on a few patients, most of whom had thyrotoxicosis.

REVIEW OF THE LITERATURE

Effect of Ergotamine on the Metabolic Rate.—Adlersberg and Porges, who were the first to report the use of ergotamine in thyrotoxicosis,[11] merely stated that the metabolic rate was reduced. Since then a number of papers have dealt with the effect of this drug on the basal metabolism, but for the most part these have been reports of poorly controlled experiments, mostly on patients with thyroid disease observed during a course of long continued and often varied treatment. In most instances no experimental data are given. In their second paper,[12] Adlersberg and Porges reported a decrease of 7 per cent in the oxygen consumption of a patient with thyrotoxicosis within an hour after the subcutaneous injection of a single dose (0.25 mg.). Under similar conditions Bouckaert and Noyons [13] observed a lowering of from 2 to 29 per cent in the basal metabolic rate of eleven patients, and LaRoche, Camus and Labourdy [14] a slight decrease (maximum 10 per cent) in five. Kerti,[15] however, noted a rise of more than 5 per cent in three patients with thyrotoxicosis and no change in one, and Halder [16] observed a slight rise in two patients from thirty to ninety minutes after the injection. Five cases are reported by Adlersberg and Porges [12] in which variable decreases in the basal metabolic rate were noted over periods of from days to months of treatment with ergotamine by mouth and subcutaneously. Halder [16] obtained similar results, but concluded that they could not with certainty be ascribed to the effect of the ergotamine. We have been able to find but three papers describing the effect of the

11. Adlersberg, D., and Porges, O.: Wien. klin. Wchnschr. **37**:327, 1924.

12. Adlersberg, D., and Porges, O.: Ueber die Behandlung des Morbus Basedowi mit Ergotamin (Gynergen), Klin. Wchnschr. **4**:1489, 1925.

13. Bouckaert, J. P., and Noyons, A. K.: Diminution du metabolisme basal sous l'influence du tartrate d'ergotamine (gynergene) chez les basedowiens, Ann. Soc. scient. de Bruxelles **46**:320, 1926.

14. LaRoche, Camus and Lebourdy: Le tartrate d'ergotamine chez les basedowiens et chez les hypersympathicotoniques, Rev. franç. d'endocrinol. **6**:52, 1928.

15. Kerti, F.: Die Einwirkung von Phlorrhizin und Gynergen auf den respiratorischen Stoffwechsel und ihre gegenseitige Beeinflussung, Wien. klin. Wchnschr. **41**:1119, 1928.

16. Halder, M.: Ueber den Einfluss des Ergotamins auf den Grundumsatz Basedowkranken, Schweiz. med. Wchnschr. **57**:411, 1927.

drug in normal subjects. Kerti [15] found a decrease in the metabolic rate in one experiment and no change in the others, while in one of Löw and Krěma's [17] normal subjects the rate fell from —8.9 to —16.2 per cent forty-five minutes after the injection of 0.5 mg. of ergotamine. Halder studied the action of the drug in three normal subjects, and in these no effect was observed following the daily administration of from 3 to 6 mg. by mouth for periods of from thirteen to twenty-nine days. It is evident from this review of the literature that previous studies fail to offer satisfactory evidence that ergotamine specifically lowers the production of heat in man.

The Effect of Ergotamine on the Pulse Rate.—As in the case of the basal metabolic rate, many studies of the effect of ergotamine on the pulse rate consist of rather general observations made on patients during the course of continued treatment with the drug (either by mouth or subcutaneously), without adequate control of other factors that may have influenced the results. Thus a gradual decrease in the pulse rate was noted by Adlersberg and Porges,[12] Porges [18] and Rütz [19] in patients with thyrotoxicosis treated over periods of from six days to two or three weeks. A drop of from 10 to 40 beats per minute was observed by the latter author following the subcutaneous administration of from 0.25 to 0.5 mg. three times daily for from six to ten days, but according to the author's tables the greatest slowing occurred shortly after the patients were placed in bed. Slowing of the pulse (maximum 21 beats per minute) in five of eight patients receiving the drug over periods of from ten to thirty days, with no effect in one and an increase in two, was reported by LaRoche, Camus and Lebourdy,[14] who observed no correlation between the duration of treatment and the effect obtained. The effect of a single injection has been studied by Bouckaert and Noyons,[13] who obtained a slowing of the pulse in five patients with thyrotoxicosis (maximum 26 beats per minute), no change in one and a slight increase in another, within an hour after the injection. Similar results were noted by LaRoche, Camus and Lebourdy,[14] while Barath,[20] using intramuscular injections, saw only a slight slowing in the majority

17. Löw, A., and Krěma, A.: Grundumsatzstudien, Wien. klin. Wchnschr. **41**:1453, 1928.

18. Porges, O.: Umfrage über die Behandlung des Hyperthyreoidismus, Med. Klin. **23**:200, 1927.

19. Rütz, A.: Ueber Vorbereitung und Nachbehandlung von Basedow Operationen mit Gynergen (Sandoz), Med. Klin. **22**:736, 1926.

20. Barath, E.: Untersuchungen über die Ergotaminewirkung bei Menschen, mit besonderer Rucksicht auf seine klinische Anwendungsmöglichkeiten bei inneren Erkrankungen, Ztschr. f. klin. Med. **104**:713, 1926.

(from 8 to 12 beats per minute) and a more marked slowing (from 25 to 35 beats per minute) only in the patients who received the largest doses (0.5 mg.) and who exhibited a severe reaction.

More careful and better controlled studies of the effect of a single injection (intravenous) were made by Zorn [21] and Wetterwald.[22] Both authors, using obstetric and gynecologic patients for subjects, obtained a marked slowing (average 40 beats per minute) following the intravenous injection of 0.5 mg. The slowing occurred within a few minutes after injection, the pulse rate returning to the preinjection level within two hours. In certain instances a coincidental slowing of the fetal pulse was observed by Zorn, who also was able to counteract the effect of ergotamine by the administration of calcium. Results similar to those of Zorn and Wetterwald were obtained by Kaufman and Kalk.[23] In Immerwahr's [24] series of patients with various nervous disorders a slowing of from 14 to 22 beats per minute followed the subcutaneous injection of a similar amount. According to Immerwahr, the injection of atrophine (1 mg.) after the ergotamine caused first a slightly greater slowing of the pulse and then a moderate increase (18 beats per minute) in the pulse rate. In a series of 120 experiments on 50 subjects, Goldman [25] observed some slowing in all, the maximum being 60 beats per minute following the intravenous injection of 0.25 mg. of the drug. During the period of nausea and vomiting induced by the drug, the pulse rate was increased. Atropine (amount ?) administered at the height of the effect of the ergotamine caused a greater slowing of the pulse. Goldman was unsuccessful in abolishing or reversing the effect of epinephrine on the pulse rate by the injection of ergotamine. Merke and Eisner [26] expressed the belief that the slowing caused by ergotamine is proportional to the rate of the pulse before injection.

Few studies have been made of the effect of ergotamine on the pulse rate of normal subjects under carefully controlled basal conditions.

21. Zorn, W.: Ueber die Wirkung von Gynergen auf Blutdruck und Puls beim Menschen, Klin. Wchnschr. **6**:204, 1927.

22. Wetterwald, M.: Ueber die intravenöse Darreichung des Gynergens (Ergotamintartrat), Schweiz. med. Wchnschr. **57**:292, 1927.

23. Kaufman, F., and Kalk, H.: Experimentelle Untersuchungen zur pharmakologischen Wirkung des Ergotamins, Ztschr. f. d. ges. exper. Med. **36**:344, 1923.

24. Immerwahr, P.: Ueber die Wirkung des Ergotamin auf Puls, Blutdruck und Blutzucker und ihre Beeinflussung durch Atropin, Med. Klin. **23**:1693 (Nov. 4) 1927.

25. Goldman, M., Jr.: Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, Arch. d. mal. du cœur **21**:204, 1928.

26. Merke, F., and Eisner, W.: Der Einfluss des Ergotamins auf das Elektrokardiogramm beim Hyperthyreoidismus, Deutsche Ztschr. f. Chir. **210**:239, 1928.

Barath [20] and Goldman,[25] whose studies have been referred to did not distinguish between their results in normal subjects and those in patients. Halder [16] was unable to obtain a slowing of the pulse in normal persons receiving the drug by mouth over long periods.

To summarize, ergotamine has been shown to cause a marked reduction in the pulse rate of patients when given intravenously in maximum doses. Smaller amounts and administration by the subcutaneous method cause a less marked slowing, while the evidence in favor of a significant effect of the drug when given by mouth to patients is unsatisfactory. Studies of its effect on the pulse rate of normal subjects under carefully controlled basal conditions have not been reported.

The Effect of Ergotamine on the Blood Pressure.—The effect of ergotamine on the blood pressure of human subjects has been studied by several writers, most of whom have used patients as subjects. Barath,[20] who studied the effect both in patients and in normal subjects under basal conditions, but who did not distinguish clearly between his results in the two groups, found a variable effect depending on the initial level. In subjects with normal pressures there was usually a slight drop (from 10 to 15 mm. systolic) often preceded by an initial rise of short duration, but in some subjects there was no change. Patients with hypertension showed the greatest lowering (from 30 to 35 mm. systolic), with a slight rise in the diastolic pressure. On the contrary, Immerwahr,[24] in a series of patients, both those with normal endocrine and nervous systems and with various nervous and endocrine disorders, found a slight rise in the blood pressure in both normal subjects and those with hypertension, while in those with hypotension the pressure was slightly lowered, returning to the initial level in from thirty to sixty minutes. The injection of atropine (1 mg.) was followed by a significant drop in about five minutes, even in persons whose pressure was elevated by the ergotamine. According to Zorn,[21] the administration of 0.5 mg. intravenously to obstetric and gynecological patients with a normal circulation and nervous system caused an increase of about 40 mm. systolic which appeared in about forty minutes and disappeared in an hour or more. Increases in both systolic and diastolic pressures (from 20 to 60 mm.) were noted by Kaufman and Kalk [23] following the intravenous injection of from 0.25 to 0.5 mg. of ergotamine. Rütz [19] noted a variable decrease in the blood pressure of eleven patients with thyrotoxicosis treated over a period of from six to ten days with from 0.125 to 0.25 mg. of the drug subcutaneously, but did not control other factors that may influence the results. It is thus apparent that the reported effects of ergotamine on the blood pressure in man differ widely.

The Effect of Ergotamine on the Blood Sugar.—Few studies have been made of the effect of ergotamine on the blood sugar level of fasting normal subjects. More often patients with various diseases have been used as subjects. Frequently ergotamine has been employed in experimental studies of the relation between the sympathetic nervous system and carbohydrate metabolism on the assumption that with ergotamine the action of the former could be abolished or modified. Seidel [27] observed a slight drop in the blood sugar of fasting normal men, but, according to Barath,[20] a more or less outspoken rise occurs in the majority, with no significant change in a few. Czezowska and Goertz [28] found an increase and Moretti [29] found no significant change under similar conditions. Immerwahr [24] obtained a biphasic response, a slight initial drop being followed by a small increase. The injection of atropine with the ergotamine made no difference in the response. In a group of patients, Goldman [25] obtained a drop in the majority, and Löw and Krěma [17] found a fall in two coincident with a decrease in the basal metabolism. In ten patients with diseases of the eyes Michail, Bendescu and Vancea [30] saw only a slight drop in three, each of whom had a rather high fasting level. Several writers reported a decrease in the blood sugar in diabetic persons following the injection of ergotamine (Seidel, Moretti and Goldman), and a similar effect was noted in patients with other diseases, particularly thyrotoxicosis (by the foregoing authors and by Rothschild and Jacobsohn [31]). On the other hand, Grunke [32] found no effect in patients with various diseases, including diabetes, and Czezowska observed an increase in patients with exophthalmic goiter. Corbini [33] concluded that ergotamine has almost no effect on the hyper-

27. Seidel, W.: Die Wirkung des Ergotamins (Gynergen) auf den Blutzuckerspeigel beim Kaninchen und beim Menschen, Arch. f. exper. Path. u. Pharmakol. **125**:269, 1927.

28. Czezowska, Z., and Goertz, F.: Influence de l'ergotamine sur le taux du sucre sanguin, Compt. rend. Soc. de biol. **98**:148, 1928.

29. Moretti, H.: L'action hypoglycemiante de l'ergotamine dans le diabète, Compt. rend. Soc. de biol. **97**:320, 1927; Glykämin und Ergotamin, Klin. Wchnschr. **7**:407, 1928.

30. Michail, D.; Bendescu, T., and Vancea, P.: Action de l'ergotamine sur le metabolism basal et la glycémie dans les affections oculaires, Compt. rend. Soc. de biol. **98**:1468, 1928.

31. Rothschild, F., and Jacobsohn, M.: Die Wirkung von Ergotamin (Stoll) beim Basedow und im Tierversuch auf die Blutzusammensetzung, Ztschr. f. klin. Med. **105**:406, 1927.

32. Grunke, W.: Ueber den Mechanismus der alimentären Hyperglykämie: I. Mitteilung. Der Einfluss des vegetativen Nervensystems auf die alimentäre Hyperglykämie, Ztschr. f. d. ges. exper. Med. **52**:488, 1926.

33. Corbini, G.: Azione dell'ergotamina sulla glicemia digli individui normali, epatici e diabetici, Policlinico (sez. prat.) **37**:85, 1930.

glycemia in otherwise normal persons and in patients with hepatic disorders. In diabetic persons, it has a tendency to lower the blood sugar, but the intensity of this action varies greatly in individual cases.

According to Loewenberg,[34] ergotamine depresses the alimentary hyperglycemia in normal subjects when small amounts of dextrose are used, and Czezowska [28] found that the alimentary hyperglycemia was diminished both in normal subjects and in those with diabetes. Moretti,[29] however, was unable to obtain any effect on the alimentary hyperglycemia of normal subjects, although the increase in blood sugar after the injection of epinephrine was decreased (or prevented?) by ergotamine. A similar effect on hyperglycemia due to epinephrine was noted by Coelho and de Oliveira,[35] and depression of alimentary hyperglycemia in normal subjects or patients was found by Grunke,[32] Hetenyi and Pogany [36] and Rednik.[37] It is thus apparent that contrary results have been obtained in respect to the effect of ergotamine on the blood sugar of fasting normal subjects though there is general agreement that it lowers the blood sugar in persons with diabetes, and the majority of observers have noted a lessening of alimentary hyperglycemia in both normal subjects and patients.

EXPERIMENTAL DATA

The normal subjects were nine healthy, young adults accustomed to the procedures employed, which probably accounted for the low basal metabolic rates found in some of them. The following plan was generally followed: About six hours after a light breakfast, the subject was placed in a bed and allowed to rest quietly for at least an hour before beginning the experiment. Following the rest period there was a preliminary period of about thirty minutes during which the pulse and blood pressure were determined at frequent intervals, until a constant level was reached. At the end of this period the basal metabolism was determined, following which a sample of blood was drawn for the determination of blood sugar. After a short rest to allow the subject to recover from the slight disturbance caused by the metabolism test and venipuncture, 0.5 mg. of ergotamine (ergotamine tartrate, Sandoz) was injected subcutaneously. Repeated determinations of the basal metabolic rate, pulse rate, blood pressure and blood sugar were made over a subsequent period of three hours. Readings of the pulse rate and blood pressure were made at intervals of five minutes, during the first half hour and at intervals of from ten to twenty minutes during the subsequent

34. Loewenberg, R. D.: Pharmakologische Beiträge zur Frage der alimentären Glykämie, Ztschr. f. d. ges. exper. Med. **56**:147, 1927.

35. Coelho, E., and de Oliveira, J. C.: Influence de l'ergotamine sur l'hyperglycémie alimentaire chez les sujets normaux et chez les diabétiques, Compt. rend. Soc. de biol. **99**:1527, 1928.

36. Hetenyi, S., and Pogany, J.: Ueber den Mechanismus der alimentären Hyperglykämie, Klin. Wchnschr. **7**:404, 1928.

37. Rednik, T.: Die Beeinflussung der Medikamente auf die Dextrose Belastungs Blutzuckerkurven als Leberfunktionsprüfung, Ztschr. f. klin. Med. **109**:720, 1928-1929.

period. The metabolic rate was determined at hourly intervals, and the blood sugar was determined in some cases at intervals of thirty minutes, one, two and three hours after the injection of ergotamine. In others the blood sugar was first determined at fifteen instead of thirty minutes after the injection and the three hourly periods omitted. In additional experiments three of the subjects were given atropine (1.3 mg. subcutaneously) before or after the injection of ergotamine, and its influence on the response to the latter was determined as already outlined. In the experiments with atropine and ergotamine an attempt was made to time the injections so that the periods of maximum effect of the drugs, determined by control experiments, coincided. Control experiments were performed with each subject, and the behavior of the metabolic rate, pulse rate, blood pressure and blood sugar, without the injection of ergotamine, was noted over a similar period of time. In the case of the subjects in the experiments with atropine, control experiments were performed in which the effect of atropine alone on the pulse rate was observed.

Three of the subjects were given 1 mg. of ergotamine by mouth three times a day over a period of eight days, and the basal metabolic rate was determined every second day in the morning under standard basal conditions.

Essentially the same plans were followed in the case of patients and, in some, similar control experiments were made. In addition, several preliminary determinations of the basal metabolic rate alone were made to accustom the subject to the test.

The majority of the determinations of the basal metabolism were made by means of a spirometer and an analysis of the expired air according to the method of Haldane. In a few of the earlier experiments, a Roth-Benedict apparatus was used. Subsequent experiments confirmed the results obtained with the latter method. The pulse rate was counted with a stop watch, and whenever possible was counted for a full minute. In no case were there irregularities of the heart beat (except slight sinus arrhythmia) which might have caused errors in the count. The blood pressure was determined by the auscultatory method with a mercury sphygmomanometer. Determinations of the blood sugar were made according to the method of Folin.[38]

In such experiments as these, the importance of slight stimuli and their effect on the pulse rate and blood pressure of subjects in a basal condition is often not sufficiently appreciated. Even with trained subjects, slight motion, anticipation of a painful injection, the entrance of persons into the room and similar disturbances are reflected in changes in these functions. The effect on the metabolic rate (except at the time of testing) is less important. In experiments in which readings of the pulse and blood pressure are made at frequent intervals, such changes may overshadow the effects of a drug, and it is necessary to allow for such temporary variations in accounting for the effect obtained.

Certain features of the reaction to ergotamine, particularly the subjective symptoms, should be noted. The injections themselves are painful, but curiously enough seem to be less painful to patients with thyro-

38. Folin, O.: Laboratory Manual of Biological Chemistry with Supplement, New York, D. Appleton & Company, 1925, p. 308.

toxicosis than to the normal subjects; at least the patients complained less than did the latter. No other immediate ill effects were noted from the injections. Nausea was frequently experienced about thirty minutes after the injection, and vomiting occurred in one normal subject and in one of the patients. In some additional experiments, not reported here, in which ergotamine was given subcutaneously and dextrose by mouth to patients with thyrotoxicosis, vomiting invariably occurred. A dull headache was often noticed within an hour or so after the injection, and about two hours after the injection of ergotamine pain and soreness developed in the muscles. This soreness, which was particularly notice-

TABLE 1.—*Effect of Ergotamine (0.5 Mg. Subcutaneously) on the Basal Metabolic Rate of Normal Subjects*

Subject		Basal Rate Before Ergotamine, per Cent	Basal Metabolic Rate After Ergotamine		
			First Hour, per Cent	Second Hour, per Cent	Third Hour, per Cent
H. F.	Test	+12	— 3	± 0	— 2
	Control*	+ 5	— 1	+ 2	— 9
J. Y.	Test	—19	—21	—19	—14
	Control	—23	—19	—24	—21
W. T.	Test	— 1	— 7	— 8	—
	Control	— 2	— 1	— 2	— 5
F. J.	Test	— 2	— 5	+ 5	—
	Control	— 1	+ 4	+ 7	+10
M. T.	Test	— 1	— 5	—10	— 8
	Control	— 7	—12	—10	—14
V. B.	Test	+ 5	+ 6	+ 5	+13
	Control	—	—	—	—
A. C.	Test	— 2	— 7	— 6	+ 3
	Control	+ 3	....	— 1	± 0
E. J.	Test	—14	—18	— 7	— 1
	Control	—11	....	— 5	— 6
M. D.	Test	+ 5	— 3	— 3	+ 2
	Control	— 1	....	— 3	— 6

* Control experiments over the same period of time without ergotamine.

able on walking, persisted and was frequently more severe the day after the experiment. Lassitude and a lack of energy were associated with this soreness; in the subjects who received the drug by mouth this effect was sufficient to cause an interference with their usual activities for two or three days after the drug had been taken. The patients with thyrotoxicosis seemed to suffer much less from the muscular soreness and the lassitude than did the normal subjects and rarely complained, though the normal subjects complained bitterly.

RESULTS

In none of the nine normal subjects was a significant effect on the basal metabolic rate noted during the three hours following the injection of the ergotamine (table 1). A slight increase (maximum 8 per

cent) occurred at the end of the third hour in three of the subjects and may probably be attributed to restlessness. In seven of the subjects, including the three in whom a rise occurred, there was a variable drop (maximum 9 per cent) at some period after the injection, but in no case were the variations greater than those observed in the control experiments. In the case of the single subject (H. F.) in whom an apparently significant drop occurred, subsequent experiments indicated that the initial determination was not made under basal conditions. The injection of atropine before or after the ergotamine failed to influence the effect of the latter on the basal metabolism.

In all of the subjects the injection of ergotamine was followed by a slowing of the pulse, which was slight in some but probably definite

TABLE 2.—*Effect of Ergotamine (0.5 Mg. Subcutaneously) on the Pulse Rate and Blood Pressure of Normal Subjects* *

	Pulse Rate per Minute		Blood Pressure (Mm. of Mercury)			
			Systolic		Diastolic	
Subject	Before Ergotamine	After Ergotamine	Before	After	Before	After
H. F.	80	74	122	124	72	82
J. Y.	76	54	98	100	72	78
W. T.	76	60	110	120	70	86
F. J.	90	78	104	106	66	68
M. T.	76	64	108	114	62	80
V. B.	64	58	112	122	70	88
A. C.	71	64	86	96	58	78
E. J.	69	63	96	112	56	90
M. D.	75	65	110	118	64	80

* The figures for pulse and blood pressure before the administration of ergotamine represent the last reading before giving the drug when these figures were consistent with the general basal level, otherwise the last basal reading. The figures for the pulse after the administration of ergotamine represent the lowest rate recorded, and for the blood pressure, the highest recorded, when apparently not due to the disturbing factors to which reference is made in the body of the paper. The control pulse rate in the case of subject F. J. is probably not basal.

in all (table 2). The maximum slowing was 22, the minimum, 6 beats per minute below the basal rate. This slowing of the pulse appeared most often about thirty minutes after the injection, and as a rule the rate gradually returned to normal by the end of three hours. In many of the experiments the slowing of the pulse was associated with the appearance of a respiratory sinus arrhythmia, and in the few instances in which this arrhythmia was present before injection it was increased during the period of bradycardia. In the experiments in which atropine was given before the ergotamine no effect of the latter on the pulse rate was noted, and the increase in pulse rate was as great as in the control experiments in which atropine alone was given. When atropine was given after the pulse had been slowed with ergotamine, the effect due to the latter was immediately abolished, and again the pulse became as rapid as it did with atropine alone (table 3).

The injection of ergotamine caused an increase in the blood pressure in nearly all of the experiments (table 2). The increase was greatest (maximum 34 mm.) in the diastolic pressure and usually appeared about thirty minutes after the injection. A less striking (maximum 16 mm.) and somewhat more variable response was noted in the case of the systolic pressure. These changes in the blood pressure persisted for some time, and the previous level was attained by gradual stages about three hours after the injection. In general the greatest effect on the blood pressure occurred in the subjects showing the greatest changes in the pulse rate, and it is interesting that these subjects were

TABLE 3.—*Effect of Atropine on the Response of the Pulse Rate to Ergotamine in Normal Subject (H. F.): Comparison with Effect of Atropine Alone* *

Atropine and Ergotamine	Time	Atropine
84	2:00	74
80	2:05	72
82	2:10	72
86	2:20	74
Ergotamine 0.5 mg.	2:21	Atropine 1.3 mg.
81	2:25	80
80	2:30	84
76	2:35	92
Atropine 1.3 mg.	2:36	..
68	2:40	92
78	2:45	94
88	2:50	94
90	2:55	94
94	3:00	94
94	3:05	96
94	3:10	96
96	3:20	98
96	3:30	98
94	3:40	90
90	3:50	85
92	4:00	85
90	4:10	82
88	4:20	80
84	4:30	80
82	4:50	88
86	5:10	78
84	5:20	74

* In this table the experimental data have been adjusted to a common time basis.

considered to have the most labile nervous systems. A typical protocol showing the effect on the pulse rate and the blood pressure is given in table 4. It should be noted that temporary variations, due to the causes mentioned, tended to obscure the effect of the drug, particularly in the cases in which the effects of the drug were slight. In two of the subjects, the injection of both atropine and ergotamine resulted in a greater rise in blood pressure, both systolic and diastolic, than when ergotamine alone was used.

Ergotamine had no significant effect on the blood sugar level in these experiments, and the slight variations above and below the initial level were no greater than occurred in the control experiments and are believed to lie within the range of normal variation (table 5).

At some time after the injection, all of the subjects showed an increase over the initial value (maximum 10 mg. per hundred cubic centimeters), and in seven subjects there was also a fall (maximum 8 mg.).

TABLE 4.—*Effect of Ergotamine on the Pulse Rate and Blood Pressure in a Normal Subject (M. D.)*

Time	Pulse Rate Beats per Minute	Blood Pressure (Mm. of Mercury) Systolic	Diastolic	Comment
1:14	76	106	60	
1:20	75	106	64	
1:22	78	110	66	
1:25	76	108	66	
1:28	76	112	68	
1:30	76	110	64	
1:31	..	...	..	Metabolism test
1:40	78	...	..	
1:50	75	118	74	
2:00	..	...	..	Electrocardiogram
2:08	..	108	76	Venipuncture
2:09	Ergotamine 0.5 mg. subcutaneously			
2:12	72	108	70	
2:15	69	110	70	
2:20	69	106	60	
2:25	69	108	70	
2:30	70	114	74	Feels "queer"
2:35	65	110	70	
2:40	68	110	74	Venipuncture
2:45	69	118	80	
2:50	69	118	80	
2:55	65	116	70	
3:00	..	118	76	Metabolism test
3:12	..	...	..	Venipuncture
3:20	..	...	..	Electrocardiogram
3:23	..	100	64	
3:30	76	112	66	
3:40	67	112	68	
3:50	69	110	72	Pain in muscles
4:00	69	114	72	
4:01	..	...	..	Metabolism test
4:09	..	...	..	Venipuncture
4:10	68	116	70	
4:25	70	112	64	
4:40	70	114	74	
5:05	70	110	74	Metabolism test
5:10	78	108	68	

TABLE 5.—*Effect of Ergotamine (0.5 Mg. Subcutaneously) on the Fasting Blood Sugar Level of Normal Subjects*

Subject	Before Ergotamine	Blood Sugar (Mg. per 100 Cc.) After Ergotamine 15 Minutes	30 Minutes	60 Minutes	120 Minutes	180 Minutes
H. F.	73	69	73	73	82	..
J. Y.	93	91	99	90	93	..
W. T.	76	76	76	76	83	..
F. J.	64	64	63	68	65	..
M. T.	74	74	66	83	77	..
V. B.	85	..	86	86	88	84
A. C.	87	..	87	91	91	95
E. J.	77	..	76	81	75	78
M. D.	66	..	69	64	66	..

No change in the basal metabolic rate occurred in any of the three subjects who were given ergotamine by mouth (table 6). It was noted, however, that the respiratory quotients showed a tendency to drop toward the end of the experiment.

In general, the effect of ergotamine on the basal metabolic rate of patients with thyrotoxicosis was similar to that seen in the normal subjects (table 6). The effect on the pulse rate, however was more marked, and greater changes were seen more often. In no case did the drug fail to cause a definite increase in the diastolic pressure, and the effect on the systolic pressure was much more marked than in the normal subjects (table 7). In two subjects (J. B. and N. R.) in whom the diagnosis of thyrotoxicosis was doubtful, the changes in pulse rate

TABLE 6.—*Effect of Ergotamine (0.5 Mg. Subcutaneously) on the Basal Metabolic Rate of Patients with Thyrotoxicosis*

Subject	Basal Metabolic Rate Before Ergotamine, per Cent	Basal Metabolic Rate After Ergotamine		
		First Hour, per Cent	Second Hour, per Cent	Third Hour, per Cent
J. B.	+ 2	± 0	+ 2	....
I. C.	+22	+26	+14	+22
N. R.	+ 8	− 2	+ 4	+ 7
D. C.	+79	+87	+81	+80
M. G.	+54	+50	+57	+65
E. P.	+79	+94	+83	+94
J. B.	+10	+16	+19	+20
O. H.	+54	+63	+70	+75

TABLE 7.—*Effect of Ergotamine (0.5 Mg. Subcutaneously) on the Pulse Rate and Blood Pressure in Patients with Thyrotoxicosis* *

Subject	Pulse Rate per Minute		Blood Pressure (Mm. of Mercury)			
			Systolic		Diastolic	
	Before Ergotamine	After Ergotamine	Before Ergotamine	After Ergotamine	Before Ergotamine	After Ergotamine
J. B.	76	70	110	112	74	80
I. C.	78	68	116	162	58	90
N. R.	108	93	116	130	70	76
D. C.	122	105	150	174	70	94
M. G.	100	84	140	160	80	90
E. R.	104	101	122	172	64	86
J. B.	65	56	118	148	64	80
O. H.	96	82	142	174	64	104

* See note under table 2.

and blood pressure were about as great as those in normal subjects. In four of the six patients with definite thyrotoxicosis the injection of ergotamine had no significant effect on the metabolic rate. Minor variations both above and below the initial determination occurred at some time during the experiment (maximum 11 per cent and 8 per cent, respectively). In one patient (E. R.), with an initial rate of + 79 per cent, the rate rose in the first hour to + 94 per cent, fell to + 83 per cent at the second hour and again rose to 94 per cent at the end of the third hour. In another patient (O. H.), with an initial rate of + 54 per cent, the

rate rose steadily to + 75 per cent by the end of the third hour. Of the two patients in whom the diagnosis was uncertain, a drop of 10 per cent occurred in one (N. R.) within the first hour and no change in the other. It is interesting to note that of the six patients with thyrotoxicosis a rise of greater or less degree, at some time after the injection of the drug, was noted in all. The respiratory quotients showed changes which followed the variations in the metabolic rate. Two patients (I. C. and D. C.) were given 0.25 and 0.125 mg. of ergotamine, respectively, subcutaneously, three times daily, for a period of from six to eight days. At the end of this period the basal metabolic rate remained unchanged in the first patient and had dropped from + 76 to + 63 per cent in the other, but during this time the patients were at rest in bed, under general medical treatment, and the lowered rate in the second patient may well be attributed to this nonspecific therapy.

In the case of two of the patients, determinations of the blood sugar were made as in the normal subjects. In one instance (I. C.) the blood sugar fell from 135 to 81 mg. per hundred cubic centimeters at the end of an hour, and in the other (D.C.) from 82 to 71 mg. in two hours.

COMMENT

From our experiments it seems apparent that ergotamine has little, if any, direct influence on the production of heat in normal subjects under basal conditions. This observation, which is in accord with the results obtained by us with trained, unanesthetized dogs, is the more significant in view of the numerous reports that ergotamine lowers the production of heat in both animals and man. It should be emphasized, however, that in the past few experiments have been performed with normal subjects under strict basal conditions. The majority of studies have been made with patients rather than normal persons as subjects. In either case the experimental data reported are generally incomplete, but a careful examination of the data given suggests that the supposed effect of the drug has been largely illusory and that failure to secure proper basal conditions or to evaluate and control properly other factors concerned has been responsible for the apparent effect of the drug. Nevertheless, the failure of ergotamine to influence the production of heat in normal subjects is not proof that in patients with certain abnormal conditions the drug is ineffective. Our results with patients, while strongly suggestive, are inconclusive in this respect.

The view is generally held among those who have reported a lowering of heat production by ergotamine that this result is accomplished by a paralyzing or depressant action on the sympathetic nervous system. Such an explanation might serve to explain the difference in our results

from those of others on the assumption that the abnormal activity of the sympathetic system assumed to be present in certain diseases and particularly in patients with thyrotoxicosis, made the sympathetic system more sensitive to the action of the drug. This explanation, while it receives little support from our clinical studies, cannot be dismissed and will be discussed further. There exists, however, another explanation that may serve to explain the reduction in the basal metabolic rate which is sometimes seen following the administration of ergotamine. Reference has already been made to the lassitude and feeling of fatigue which follow the administration of the drug, especially when it is administered over a period of several days. As a result of this, greater relaxation may be secured, particularly in patients subject to overstimulation, and with it a more nearly basal condition. In other words, although ergotamine may not possess a direct action on the production of heat, by indirect means it may permit a determination more nearly basal. A similar explanation has been offered by Merke.[39] Such an effect would of necessity vary considerably with individual subjects and is therefore in accord with the marked individual variations in response to the drug.

The failure of ergotamine to affect the fasting blood sugar level of normal subjects, again in accord with our results in trained unanesthetized dogs, is important because the reported effects on the blood sugar have also been ascribed to an action on the sympathetic nervous system. This failure to affect the blood sugar of fasting normal subjects agrees with the results of several other workers, and it seems safe to conclude that under basal conditions ergotamine is ineffective in this respect in these persons. It must again be emphasized that this conclusion applies only to fasting normal subjects, since the work of other investigators apparently shows a definite influence of ergotamine on the changes in the blood sugar in response to certain stimuli, such as the administration of epinephrine, and in patients with certain diseases. Unreported experiments of our own suggest a similar effect. This failure of ergotamine to modify the sympathetic nervous system under basal conditions and to affect it under conditions that may stimulate it is of considerable interest and will be discussed further.

The most marked effect of ergotamine was on the pulse rate and blood pressure. Similar, but greater, effects on the pulse were obtained by us on trained, unanesthetized dogs, and a number of writers have obtained results similar to ours in man, although in many instances the

39. Merke, F.: Ueber die Wirkung des Gynergens beim Morbus Basedowi, Schweiz. med. Wchnschr. **57**:833, 1927.

reported reduction in pulse rate has undoubtedly been due to factors other than the drug. This slowing of the pulse has most often been explained as a paralyzing or depressing action of ergotamine on the accelerator nerves of the heart. From the results of our experiments, both with animals and with man, we are unable to agree to this explanation. Rather, the slowing appears to us to be due to a vagus stimulation or sensitization. We do not mean by this a relative stimulation due to partial release of accelerator control, as suggested by LaRoche, Camus and Lebourdy,[14] nor a combination of accelerator depression and vagus stimulation, as suggested by Rothlin.[2] Our reasons for this belief in the case of animals have been stated elsewhere,[10] and we believe that they receive additional support from our experiments on human subjects. With man, as with dogs, small doses of atropine completely prevented or abolished the slowing due to ergotamine. After atropinization there was no evidence of a paralysis or depression, partial or complete, of the accelerator nerves, and the pulse rate was increased to as great a degree as with atropine alone. Hamet[40] made a similar observation. Slight stimuli were sufficient to cause a distinct increase in the pulse rate after the injection of ergotamine. The action of ergotamine on the sympathetic system is known to be slow, and in our experiments a considerable time elapsed before the effect of the drug was observed, yet in animals the action was almost immediate after intravenous injection. A prompt action has been observed by those who have injected the drug intravenously in man. In our experiments the action of the drug seemed stronger in the subjects with evidence of a strong vagus tone (sinus arrhythmia). The appearance of this arrhythmia after the administration of ergotamine, when not present before the injection, is also suggestive of a vagus action. Certain of the subjective symptoms, such as nausea and vomiting, are in favor of a vagal effect. Finally, in view of the large amounts of ergotamine that are known to be necessary to affect the accelerator nerves in animals, the doses that can be used clinically would scarcely seem sufficient to produce the decided slowing of the heart observed in man, by a depression of the accelerator nerves. The belief that ergotamine slows the heart by an action of the vagus has also been expressed by Wetterwald.[22]

The increase in blood pressure in the normal subjects was of about the same magnitude as the changes in the pulse rate and was probably due to the same mechanism by which ergotamine causes a rise in blood pressure in animals. A primary blood pressure raising (vasoconstrictor)

40. Hamet, R.: Les principes actifs de l'ergot et leur action pharmacologique, Presse méd. **35**:1605, 1927.

effect was observed by Dale and Spiro [41] and ascribed by them to a stimulation of the arterial musculature. According to Rothlin,[2] this effect, which may be the sole result of small as well as the initial effect of large doses, is due to a stimulation of the sympathetic ganglions. However, the effect of ergotamine on the blood pressure in animals is most variable. In addition to inhibiting and reversing the effects of epinephrine, in which marked individual and species variations occur, and the primary blood pressure raising effects described by Dale and Spiro [41] and Rothlin,[2] Salant, Nadler and Brodman [42] have observed a primary blood pressure lowering effect. This was apparently due to an associated action of the natural epinephrine in the body, since it failed to appear when the suprarenals were removed. According to Dale and Spiro,[41] the primary blood pressure raising effect of ergotamine may fail to appear if the arteries are in a state of increased tonus at the moment of injection. This may serve to explain the failure of some authors to obtain an effect when dealing with subjects (patients) in whom the pressure was already elevated. It is also possible that the observations of Salant, Hadler and Brodman may explain the fall in blood pressure obtained in some subjects, particularly those with an elevated pressure. Nevertheless, it is probable that the lowering of the blood pressure obtained by most authors with human subjects was due to a lengthening rest period and failure to secure basal readings at the start of the experiment.

The results of our experiments raise the question whether, in man, ergotamine possesses the same action on the sympathetic nervous system as has been described in animals. There can be no doubt that in animals ergotamine in sufficient dosage exerts a depressant action on many of the motor functions of the sympathetic nervous system and probably on some of the inhibitory functions as well. As we have stated many times, however, such effects are obtained in animals with doses and experimental conditions that are not permissible in the case of human subjects. The failure of ergotamine to affect certain of these functions in man may be attributed in part to the necessary use of small doses, which are ineffective. On the other hand, certain of the results observed may be attributed to the different action of small, as compared with large doses.

However, another and more significant explanation is suggested for the failure of ergotamine to affect certain functions of the sympathetic system in normal subjects under basal conditions. The work of Cannon

41. Dale, H. H., and Spiro, K.: Die Wirksamen alkaloide des Mutterkorns, Arch. f. exper. Path. u. Pharmakol. **95**:337, 1922.

42. Salant, W.; Nadler, J. E., and Brodman, K.: Circulatory Reactions to Ergotamine and Effect upon Them Produced by Adrenalectomy and the Blood *Pu*, Proc. Soc. Exper. Biol. & Med. **25**:361, 1927-1928.

and his associates [43] seems to show that in animals, under conditions of quiet and repose (i.e., basal conditions), certain functions of the sympathetic system are inoperative. Cannon's view, which is somewhat opposed to the theory of a constant activity of the sympathetic system balanced against the parasympathetic system, postulates a condition of homeostasis which may be modified on need by the sympathetic system, which is called into play when the need arises. "One may consider total inactivity of the exterofective system as a basal state for the organism, i.e., a condition for minimal functioning of both the exterofective and enterofective systems. Whenever the exterofective system becomes active an internal disturbance is produced or tends to be produced, and associated therewith the basal enterofective function is increased in order to maintain homeostasis. It should be clear from the foregoing considerations that if the organism is maintained in a fairly constant basal condition, i.e., if there is not marked disturbance of the internal environment because of response to external stimuli, there is relatively little need for the functioning of the enterofective system." On the basis of such an hypothesis it is not surprising that ergotamine, granting it is a depressant of the sympathetic system, should fail to exhibit any effect on certain functions of the latter under basal conditions. The functions of a mechanism that is inoperative can scarcely be depressed or paralyzed. The best evidence in favor of this explanation for the ineffectiveness of ergotamine is its effect on the blood sugar. The failure of ergotamine to affect the accelerator nerves of the heart, which, in contrast to other parts of the sympathetic system, may be assumed to be in a state of constant activity, need not of necessity conflict with this explanation in view of the well known resistance of these nerves to small doses of ergotamine. In fact, this resistance of the accelerator nerves may be related to the degree of their tonicity. Analysis of the experimental evidence in respect to the action of ergotamine suggests that it is the weaker sympathetic functions that are the more readily affected by the drug. Such a possibility may explain why ergotamine, although it fails to lower the production of heat of normal subjects, because of the relative inactivity of the sympathetic system under basal conditions,[44] fails also in some instances when the production of heat is increased above the basal level by the action of the

43. Cannon, W. B.: Organization for Physiological Homeostasis, Physiol. Rev. **9**:399, 1929; The Sympathetic Division of the Autonomic System in Relation to Homeostasis, Arch. Neurol. & Psychiat. **22**:282 (Aug.) 1929.

44. Cannon, W. B.; Newton, H. F.; Bright, E. M.; Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, Am. J. Physiol. **89**:84, 1929.

sympathetic system. It is conceivable that under the latter conditions the tonicity of the sympathetic system may be so great as to make it relatively insusceptible to the amounts of the drug that can be used. Thus may be explained the conflicting results on the basal metabolism which have been obtained clinically in some disease states.

In the case of the rise in blood pressure seen in normal subjects under basal conditions, the absence of activity of the sympathetic system is of no significance, since the effect is apparently due to the vasoconstrictor or stimulant action of small doses of ergotamine, as previously stated. The reported lowering of the blood pressure in some abnormal subjects may be the result of the action of the drug on a sympathetic function which is active. Failure to secure a reduction in some patients with an elevated pressure, as in some of our patients with thyrotoxicosis, may be due to a relatively too great tonus of the sympathetic system.

The explanation that we have suggested would serve not only to account for the behavior of ergotamine as observed in our experiments, but also to explain many of the apparently conflicting results which appear in the literature on ergotamine. The results of some additional but uncompleted studies seem to offer further evidence in its support. Should this explanation prove to be correct, our results offer some evidence that in man the function of the sympathetic system is similar to that described by Cannon in animals.

The reaction to the drug, especially the muscular soreness and fatigue, is of some interest. While no adequate explanation for these symptoms is to be found in our experiments, it is suggested that the muscular soreness may be the result of the action of the drug on the smaller arteries and the arterioles of the muscles, causing a relative and temporary ischemia. Such a possibility is of interest in view of the gangrene which is a characteristic feature of the toxic action of ergot (and ergotamine). Neither gangrene nor any other serious untoward effect was observed in any of the normal subjects or patients, although some of the latter were given ergotamine over considerable periods of time. Toxic symptoms, including gangrene, have, however, been reported in patients who were treated with ergotamine.[45]

SUMMARY AND CONCLUSIONS

Ergotamine, in single doses of 0.5 mg. subcutaneously, was without significant effect on the basal metabolic rate or fasting blood sugar level of normal human subjects. The pulse rate was slowed, and the blood

45. Schönbauer, L.: Zur Behandlung des Morbus Basedowi mit Ergotamin (Gynergen), Deutsche Ztschr. f. Chir. **198**:99, 1926.

pressure, the diastolic pressure in particular, was slightly but definitely elevated.

The administration of 1 mg. of ergotamine by mouth, three times daily, over a period of several days, also failed to influence to a significant degree the basal metabolic rate of these subjects.

Similar effects were noted in patients with thyrotoxicosis, although the effect on the pulse rate and blood pressure was generally greater. A somewhat greater individual variation in the response of the pulse rate and blood pressure to ergotamine was noted among the patients than among the normal subjects.

It is suggested that the failure of ergotamine to influence certain functions of the sympathetic system is due to the fact that in normal subjects under basal conditions these parts of the sympathetic system are inoperative and are therefore insusceptible to the action of ergotamine. This explanation, if correct, may serve to explain certain conflicting reports appearing in the literature. However, many of the reported instances of lowered heat production, pulse rate and blood pressure following the administration of ergotamine should not be attributed to the action of the drug, but to failure to secure a truly basal condition at the beginning of the experiment.

Under the conditions of our experiments, the slowing of the pulse cannot be attributed to a depression or paralysis of the accelerator nerves of the heart, but is the result of a stimulating or sensitizing action on the vagus.

PELLAGRA SECONDARY TO BENIGN AND CARCINOMATOUS LESIONS AND DYSFUNCTION OF THE GASTRO-INTESTINAL TRACT

REPORT OF THIRTEEN CASES *

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Pellagra as a complication of a lesion or of dysfunction of the digestive tract is assuming greater significance in view of the increasing number of cases reported. Rolph [1] first called attention to the possibility of pellagra originating under these circumstances in 1916, when he reported a case of carcinoma of the upper third of the stomach, involving the cardiac orifice and associated with pellagra. Other instances of benign and malignant lesions with secondary pellagra have been reported by Bryan,[2] Bender,[3] Nuzum,[4] Joyce and Seabrook,[5] Barnes,[6] Elliott,[7] Klauder and Winkelman,[8] Cabot [9] and one of us

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1. Rolph, F. W.: Cancer of the Stomach and Pellagra in the Same Patient, Canad. M. A. J. **6**:323 (April) 1916.

2. Bryan, R. C.: Cancer of the Stomach with Associated Pellagra, Virginia M. Monthly **46**:107 (Aug.) 1919.

3. Bender, W. L.: Pellagra Secondary to Lesions of the Stomach Interfering with Nutrition, J. A. M. A. **84**:1250 (April 25) 1925.

4. Nuzum, F. R.: Pellagra Associated with Annular Carcinoma of the Terminal Portion of the Ileum, J. A. M. A. **85**:1861 (Dec. 12) 1925.

5. Joyce, T. M., and Seabrook, D. B.: Stricture of the Rectum as an Indirect Cause of Pellagra, Northwest Med. **24**:284 (June) 1925.

6. Barnes, J. M.: Typical Pellagra Syndrome Developing in a Patient with Chronic Ulcerative Colitis While Under Hospital Treatment, Ann. Clin. Med. **4**:552 (Jan.) 1926.

7. Elliott, A. R.: Pellagra Secondary to Carcinoma of the Colon, M. Clin. North America **11**:237 (July) 1927.

8. Klauder, J. V., and Winkelman, N. W.: Pellagra Among Chronic Alcoholic Addicts, J. A. M. A. **90**:364 (Feb. 4) 1928.

9. Cabot, R. C.: A Case with Anasarca, Cyanosis, Symmetrical Dermatitis, Diarrhea, Mass in the Abdomen and Psychosis, Boston M. & S. J. **197**:1319 (Jan. 12) 1928.

(P. A. O'L.).[10] One of the most recent contributions from the pellagrous belt is that of Turner,[11] in which he reported sixteen cases of the disease associated with diverse lesions of the gastro-intestinal tract, eight of which were strictures of the rectum. One of the purposes of this report is to bring up to date the reports of cases that have come under our observation.

The diagnostic and therapeutic significance of the secondary forms of pellagra and the serious prognostic significance of the complication in the event an operation is contemplated are of immediate concern to the internist. Undoubtedly a number of cases of secondary pellagra have been encountered that have not been reported; others probably have been overlooked, including cases in which there are constitutional symptoms but no cutaneous manifestations of the disease, that is, pellagra sine pellagra.

The fact that the disease may develop as the result of obstructive gastro-intestinal lesions, of voluntary restriction of food for various reasons or of chronic alcoholic addiction, as emphasized by Klauder and Winkelman, Sweitzer[12] and Shattuck,[13] is the explanation for its distribution without geographic limit and its appearance as a complicating factor often when least expected. This is in contrast to the primary idiopathic form of the disease, which is limited to the southern states, Central America, Mexico and to such outlying possessions of the United States as the Canal Zone.

In the classic case, there are characteristic lesions of the skin, mouth and tongue, provoking sore tongue and often dysphagia, gastro-intestinal disturbances in the form of abdominal pain or discomfort, diarrhea, proctitis, often nausea and vomiting and symptoms referable to the central nervous system. The convenient diagnostic triad of dermatitis, diarrhea and dementia is more alliterative than scientific, for the dementia may appear only in the advanced stages of the disease.

Those who are familiar with the disease advise considering the possibility of pellagra in cases of chronic gastric disturbance with vernal exacerbations; when obscure abdominal symptoms referable to the appendix, ovaries or gallbladder are present; in cases of dysentery, neurasthenia, melancholia, eczema, sunburn or chapping of the arms, face, neck or feet and in cases of persistent dizziness, epileptiform seizures and vaginitis. The dermatologists recommend that when one

10. O'Leary, P. A.: Secondary Types of Pellagra, M. Clin. North America **10**:647 (Nov.) 1926.

11. Turner, R. H.: Pellagra Associated with Organic Disease of the Gastro-Intestinal Tract, Am. J. Trop. Med. **9**:129 (March) 1929.

12. Sweitzer, S. E.: Pellagra and Alcoholism, Minnesota Med. **11**:719 (Nov.) 1928.

13. Shattuck, G. E.: Scurvy, Pellagra and Sprue at the Boston City Hospital, New England J. Med. **199**:986 (Nov. 15) 1928.

is confronted with a patient complaining of obscure constitutional symptoms, one should not be satisfied until all cutaneous lesions, when any are present, have been carefully differentiated. Unsystematic or hurried examinations, failure to elicit a history of "sunburn" in suspicious cases and unfamiliarity with the appearance of the residual cutaneous lesions may make it difficult for the internist to interpret the associated phenomena. As a matter of fact, the dermatologist's recognition of the pellagrous nature of the lesions or residues in their various types and stages on several occasions has led to the disclosure of gastro-intestinal lesions in patients not residing in the pellagrous zone or the discovery of lesions which previously had escaped the notice of the examining physician. Moreover, as illustrated in three of Turner's cases, the clinician may overlook gross organic disease in the upper part of the digestive tract in the presence of a well established case of pellagra. Such an error would seem more excusable in localities where the disease is endemic.

In a previous report, one of us (P. A. O'L.)[14] showed that in the type of pellagra encountered at this clinic the dermatitis has not been so extensive or so severe as that usually observed in pellagrous districts. The well defined limitation, particularly about the wrists and the forearms, suggesting the term "gauntlet" or "glove" dermatitis, is highly characteristic of the disease, as are the well defined borders of hyperkeratosis and the residual pigmentation on the face and neck. In the acute phase the eruption may vary from blotchy erythema to extensive bullous lesions, with associated edema, whereas, in the latent and receding stages, a dry, scaling and, at times, keratotic eruption may be seen. Residual pigmentation at the periphery of the lesion is a characteristic feature of the less acute forms. Casal's "necklace," dermatitis of the anterior part of the neck, is often of diagnostic aid. Secondary infection, fissuring and ulceration may be unpleasant complications.

The recognition of pellagra is not difficult if the general symptoms that arise from involvement of the skin, the gastro-intestinal tract and the nervous system are borne in mind. From the dermatologic point of view, chronic eczematoid dermatitis, allergic dermatitis, erythema solare, erythema multiforme, lupus erythematosus of the disseminate type and ringworm must be excluded in the differential diagnosis. The problem is not difficult if the other characteristics of pellagra are demonstrable. The dermatitis, with the exception of the form pellagra sine pellagra, is essential to the diagnosis.

In spite of extensive research and great familiarity with the clinical aspects of the disease, including exhaustive pathologic studies, an extensive review of the literature still reveals a lack of unanimity con-

14. O'Leary, P. A.: Pellagra: A Study of Thirty-Four Cases in Localities Where Pellagra Is Not Endemic, Northwest Med. **27**:319 (July) 1928.

cerning the etiology of the disease. Some of those who are familiar with the acute, active endemic forms of the disease remain unconvinced that it is purely a dietetic deficiency disease. We also have observed a small group of patients in whom the disease developed while apparently they were partaking of a well balanced diet, amply adequate in calories and vitamins. Experimental, pathologic and clinical evidence undoubtedly supports the contention of Goldberger and his co-workers [15] and of other authorities, that pellagra has its origin in a deficient dietary. Recently, Findlay [16] confirmed Goldberger's researches and concluded that when rats are fed food lacking the thermostable vitamin G (the pellagra preventive, P-P, factor of Goldberger) a condition resembling black tongue in dogs and pellagra in man results. Denton,[17] in a convincing pathologic study of twelve fatal endemic cases of pellagra in the Canal Zone, reemphasized the fact that the pathologic characteristics of the lesions of pellagra give no insight into the origin and cause of the disease. His experience showed that the disease is one in which the lesions are confined to the epithelial surfaces, without extension to the deeper tissues or organs. These lesions give no evidence of being infectious; the changes in the alimentary canal do not appear to be simple inflammatory changes, and some underlying and contributory factor must be necessary for their production. Singer and Pollock [18] and others stated that the changes in the central nervous system are likewise essentially retrograde and degenerative, and not inflammatory, in both the acute and the chronic stages. Denton also maintained that the lesions of the mouth, tongue and esophagus are the most constant and consistent lesions of the disease and, although perfectly analogous to the cutaneous lesions, are not so ephemeral. He expressed the belief that this fact argues against the photodynamic hypothesis of Jobling and Arnold,[19] which maintains that a fungus, *Aspergillus glaucus* or *Aspergillus repens,* was the indirect cause of the photosensitiveness responsible for the dermatitis, and that a deficient diet permitted an overgrowth of the organism. In Bass' [20] experience, exposure not only to sunlight but to heat, pressure, trauma and irritating chemicals is

15. Goldberger, Joseph; Wheeler, G. A.; Lillie, R. D., and Rogers, L. M.: A Further Study of Experimental Blacktongue with Special Reference to the Blacktongue Preventive in Yeast, Pub. Health Rep. **43**:657 (March 23) 1928.

16. Findlay, G. M.: Pellagra-Like Lesions Associated with Deficiency of Vitamin B_2 in the Rat, J. Path. & Bact. **31**:353, 1928.

17. Denton, James: The Pathology of Pellagra, Am. J. Trop. Med. **5**:173 (March) 1925.

18. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. **11**:565 (June) 1913.

19. Jobling, J. W., and Arnold, Lloyd: Observations and Reflections on the Etiology of Pellagra, J. A. M. A. **80**:365 (Feb. 10) 1923.

20. Bass, C. C.: Pellagra, M. Clin. North America **12**:1181 (March) 1929.

capable of producing the cutaneous lesions, especially when the cause is active at the proper stage and period of activity of the general disease. The clinical evidence supporting the theory of dietetic deficiency, especially in the secondary forms of pellagra, seems convincing and is manifest in various ways. The pellagra of patients with mental disease may be the result of an unbalanced or inadequate institutional diet or the actual refusal of food over long periods of time due to the capricious appetites of psychotic persons. It is also likely that in some cases that develop in hospitals for the mentally defective, the cutaneous lesions are slow to develop. The voluntary restriction of food as a measure of reducing weight, dietary restriction in the treatment for acne, in functional gastric disorders, in "elimination" diets to determine the food allergen, in the treatment for "intestinal toxemia," following abdominal operation in the elderly patient and for no tangible or adequate reason, as in the case reported by Carley,[21] give rise to the disease.

The development of pellagra in the presence of gastro-intestinal lesions, malignant or benign, as in the cases herewith reported, and especially in the obstructive type, is an established fact. The obstructive lesion would appear to play especially a mechanical rôle in that it prevents the ingestion or retention of sufficient food or of food containing adequate vitamins. In gastro-intestinal lesions without obstruction, as in gumma of the stomach and ulcerative colitis, the development of pellagra, even when the patient is taking highly nutritious food, as Barnes observed, may be due to actual deficiency in protein as the result of inadequate absorption and assimilation in the presence of such lesions. The continued use of alcohol over a period of several weeks or months favors the development of the secondary form of the disease through gastro-intestinal upsets, anorexia and eventual semistarvation. The important part played by dietetic imbalance or inadequacy is evidenced by the improvement, often prompt, in the less severe forms of pellagra effected by the timely institution of a proper dietetic regimen or by the surgical removal of the obstruction, if the patient survives operation. The restricted diets are composed mostly of carbohydrate, and the histories often show that patients have subsisted almost entirely, over a considerable period of time, on such combinations as "milk toast, bread and cake," "toast and crackers," "milk, ice cream and bread," "oatmeal porridge and potato soup," and other combinations of a similar nature. Several patients had not eaten fresh meat for periods as long as ten years, and they were complete strangers to fresh vegetables and fruits. The effectiveness of a proper diet, even in advanced, hopeless cases, so far as the primary lesion is concerned, is exemplified in Elliott's case, in which carcinoma of the colon recurred nine years after

21. Carley, P. S.: A Case of Pellagra Following Voluntary Restriction of Diet, J. A. M. A. **91**:879 (Sept. 22) 1928.

the original operation, and in which the pellagrous lesions were severe. These disappeared five weeks after dietetic treatment was begun, and there was no recurrence of the lesions, in spite of the fact that the patient died as the result of extensive metastasis nine months after his last admission to the hospital.

Turner cited the investigations of Rolly and Liebermeister,[22] more recently confirmed by Arnold and Brody,[23] which apparently furnish, from an experimental standpoint, certain phenomena observed in pellagrous persons. It is somewhat difficult to explain the infrequency of pellagra in the vast number of patients with obstructing, malignant and inflammatory lesions of the digestive tract who have been forced to subsist on a restricted diet in order to be comfortable. Crutchfield [24] stated that pellagra is rarely seen in patients who are not suffering from some previous contributory disease that disturbs metabolism, and Shattuck expressed the belief that although in recent years much light has been thrown on the causes of pellagra and that a great deal can now be done toward prevention and cure, much more must be learned about the gastro-intestinal secretions and the factors that influence assimilation of food in this disease. Apparently other conditions, independent of the actual gastro-intestinal lesions, in which the assimilation of food is disturbed may give rise to secondary pellagra; this is exemplified in an unusual case of nutritional disturbance with osteomalacia and tetany, reported by Constam and Partch.[25] Such observations suggest the possible causative rôle of the inadequate gastric digestion of protein as demonstrated by Castle [26] in pernicious anemia, with its characteristic achylia gastrica, and possibly in many cases of sprue. However, the depression or complete cessation of gastric secretory function could be a secondary phenomenon and not essential in pellagra as it is in pernicious anemia.

Of a total of fifty-four cases of pellagra, the majority of which were of a mild, chronic form and in which the diagnosis was confirmed by dermatologists, fractional analysis of gastric content after a test meal

22. Rolly and Liebermeister, G.: Experimentelle Untersuchungen über die Ursachen der Abtötung von Bakterien im Dünndarm, Deutsches Arch. f. klin. Med. **83**:413 (Sept.) 1905.

23. Arnold, Lloyd, and Brody, Louis: Bacterial Flora and Hydrogen Ion Concentration of the Duodenum, J. Infect. Dis. **38**:249, 1926.

24. Crutchfield, E. D.: Pellagra: With Special Reference to the Skin and Mucous Membrane, Arch. Dermat. & Syph. **17**:650 (May) 1928.

25. Constam, G. R., and Partch, W. T.: An Unusual Case of Nutritional Disturbance, Showing Symptoms of Pellagra, Osteomalacia and Tetany, Minnesota Med. **12**:40 (Jan.) 1929.

26. Castle, W. B.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: Effect of Administration to Patients with Pernicious Anemia of Contents of the Normal Human Stomach Recovered after Ingestion of Beef Muscle, Am. J. M. Sc. **178**:748 (Dec.) 1929.

disclosed the absence of free hydrochloric acid in 79 per cent. In 62 per cent of Guthrie's [27] unselected cases of pellagra, gastric hydrochloric acid was absent. In our entire group there were a few cases of achlorhydria in which it was difficult to distinguish between pellagra and pernicious anemia until the effect of an antipellagrous diet on the lesions and hemopoietic function was determined. On the basis of our experience and that of many others, it is justifiable to state that when achlorhydria is persistently present, especially when it is associated with secondary anemia, asthenia, nervous irritability and diarrhea, the possibility of pellagra should be borne in mind, whether or not a history or evidence of cutaneous lesions is obtainable. Sprue should also be considered. At the same time, it is essential to determine whether or not dietetic shortcomings are in any way responsible for the condition.

Again, reverting to the endemic forms of pellagra, one is reminded of Wilkerson's [28] belief that malnutrition is the curse of the South. To this he attributes the early physical decay of many rural southerners of both sexes. His observations as to the kind of food and the preparation of food in many homes, not excluding those of the well-to-do, should make physicians and health authorities circumspect and not take for granted the patient's statement that his diet is adequate. Wilkerson called attention to the monotony of the diet, the excess of fat often used in the preparation of meats and vegetables, especially the former, and the excessive cooking of the latter. Whether or not this has any bearing on the matter, it is interesting to note that our latest case of pellagra occurred in a young girl who lived in a nonpellagrous region, but in whom a severe case developed while she was taking a ketogenic (low carbohydrate and high fat) diet for treatment for epilepsy.

TREATMENT

It is essential to determine, if possible, and to correct the exciting factor in secondary types of pellagra. The majority of such cases are the result of malignant and benign obstructing lesions of the upper part of the digestive tract as well as of unsuccessful or unwarranted operative procedures provoking marked motor or secretory dysfunction or both. Cases of obstruction usually require surgical intervention unless the condition is obviously inoperable. However, the risk is greatly enhanced, especially in cases in which malignant growths are present or in cases with high grade obstruction of whatever nature, because adequate preoperative preparation to combat malnutrition, dehydration and alkalemia, so essential to recovery, is extremely difficult in the presence of compli-

27. Guthrie, J. B.: Pellagra: Hydrochloric Acid in the Stomach Contents, Am. J. Trop. Med. **6**:357 (Sept.) 1926.

28. Wilkerson, F. W.: Dietetic Difficulties in the South, M. Clin. North America **12**:1479 (March) 1929.

cating pellagra. An earnest but careful attempt to readjust the diet should precede any attempt to remove the lesion or the cause of the dysfunction. In the early or favorable cases it is often possible to eliminate the pellagrous manifestations by intensive dietetic measures. In our experience it is necessary, after a successful operation, to prepare for the toxemia or dementia of pellagra as soon as it is feasible, even in the milder cases, as this complication invariably occurs within from three to seven days after operation. Several cases proved fatal without marked evidence of toxemia or psychosis. In some of the cases reported, removal of the obstruction alone was largely responsible for the improvement of the pellagrous features. Apparently a great deal depends on the extent to which digestive function can again be restored within reasonable limits. Outstanding results have been accomplished in the cases in which it has been possible to establish and maintain a diet high in vitamins by means of rare lean meat, yeast, the juices of citrous fruits, strawberries, apples, grapefruit, liver, salmon, eggs, milk and cream, cod liver oil and such green vegetables as spinach, lettuce, asparagus, fresh peas, cabbage and tomatoes. As the requisites of a normal diet must also be met, enough calories to maintain the body weight and sufficient bulk to obviate constipation should be furnished. The use of wheat bread and cereals may make up for the deficiency of carbohydrate in other foods. If necessary, in the presence of an ulcerative gastric lesion the vegetables and fruits which should be served may be cooked and puréed. At times it is feasible to administer food frequently and in small amounts. Owing to the digestive disturbances present and the aversion to food which some patients have, it is essential that the physician be persistent, and, if necessary, that he urge or coerce the patient to take an adequate amount. Iron and arsenic have been recommended and used by some authorities, although they are not of much proved value. Application of bland lotions in the acute phase of the dermatitis is of value and is stimulating. Mild keratolytics may be used during the periods of latency and chronicity. Complications are treated as they arise. It might be added that the vitamin content of the food should be gradually increased, reaching the maximum in about a week, and that the patient should be kept ambulatory as much as possible, although prolonged exposure to sunlight should be avoided. It is essential to impress the patient with the possibility of recurrence and to urge that he partake of a diet rich in proteins and vitamins for several years.

Details concerning the thirteen cases are contained in the accompanying table, and in the reports of the cases. In two of the cases the diagnosis was questionable; one of the patients was an elderly man, with pyloric obstruction, the result of benign gastric ulcer, and cholecystic disease; the other patient was a woman, aged 45, with a rather

diffuse syphilitic lesion of the stomach. The evidence was suggestive enough to influence us to include them in the series. With two exceptions, all of the patients lived in the north temperate zone. The cutaneous lesions were not as marked in any case as those that occur in active, acute, endemic cases. Apparently, however, the extent of the dermatitis is not a criterion as to prognosis, for the mortality was

Pellagra Secondary to Lesions of the Gastro-Intestinal Tract

Case	Lesion or Cause of Dysfunction	Age	Sex	Duration, Months	Pellagra, Distribution of Lesions	Stomatitis and Glossitis	Diarrhea	Nervous Symptoms	Psychosis	Presence of Hydrochloric Acid	Operation	Results
1	Pyloric obstruction (duodenal ulcer)	64	M	6	Hands, wrist, face and neck	—	+	0	+	+	+	Died
2	Pyloric obstruction (carcinoma)	63	M	2	Hands, wrists and face	+	+	+	+	0	+	Died
3	Pyloric obstruction (duodenal ulcer, carcinoma)	44	M	1½	Hands and wrists	+	+	+	+	0	0	Not traced
4	Duodenal ulcer and malfunctioning gastro-enterostomy	58	F	5	Hands, wrists and face	+	+	+	0	0	+	Died
5	Duodenal ulcer and malfunctioning double gastro-enterostomy	44	M	1	Hands, wrists, forehead and nose	+	+	+	+	0	+	Cured
6	Pyloric obstruction (multiple gastric ulcers, chronic cholecystitis)	62	M	1	Hands and wrists	—	+	+	0	0	+	Died
7	Large gastric ulcer, jejunal feeding	46	F	½	Hands	+	+	+	0	+	+	Cured
8	Gastric syphilis	45	F	?	Hands and wrists	+	+	—	—	0	0	Cured
9	Esophageal structure; pyloric ulcer	33	F	¾	Hands, wrists and face	+	+	+	+	—	0	Died
10	Unnecessary gastro-enterostomy	45	M	5	Hands, wrists and face	+	+	+	0	0	0	Cured
11	Unnecessary gastro-enterostomy	48	M	4	Hands and wrists	+	0	+	+	0	+	Cured
12	Carcinoma of descending colon	55	M	1	Hands, wrists, face and neck	+	+	0	+	—	0	Died
13	Ulcerative colitis	21	F	1	Hands and wrists	+	+	+	+	—	0	Improved

high, especially in the surgical group, in spite of the fact that every precaution was taken. It is to be noted that in ten of the thirteen cases reported the lesions were benign. Of the five patients who were submitted to laparotomy, five had benign lesions, of which four were complicated and there was an unfavorable termination in all but two.

REPORT OF CASES

CASE 1.—A man, aged 64, had had gastric disturbances for a number of years, at intervals of from two to six months. The symptoms were suggestive, although not characteristic, of chronic peptic ulcer with recent obstructive features.

Prior to admission to the clinic he had been under treatment for ulcer for five weeks and had obtained considerable relief. Thirty-two years previous to admission, he had had pulmonary tuberculosis, and thirty years before admission he had undergone an operation for tuberculous fistula in ano. This was followed by a stormy convalescence, and one month later spontaneous rupture occurred, and thin, purulent material was passed, apparently from the rectosigmoid. In the summer of 1928, diarrhea was present at frequent, brief intervals. For six months prior to admission, the patient's diet was markedly reduced. He lost 20 pounds (9 Kg.). There was dark discoloration and dryness of the hands and forearms, associated with marked general weakness, moderate depression and apathy.

Examination revealed evidence of malnutrition, marked dehydration, severe oral sepsis, definite physical signs of an old tuberculous process in the upper lobe of the right lung, moderate tenderness and rigidity in the right upper quadrant of the abdomen, normal reflexes and sensations and anal scars. The skin of the gauntlet areas of both hands and wrists was sharply delineated, pigmented and slightly keratotic, but without erythema. Laboratory investigations disclosed gastric hyperacidity. There was roentgenologic evidence of deformity of the duodenal bulb, with considerable residue of barium after six hours. A few polyps of the sigmoid were seen through the proctoscope.

After preliminary preparation, posterior gastrojejunostomy was performed for a subacute, perforated duodenal ulcer and marked pyloric obstruction. A poor prognosis was given on account of the complicating pellagra. On the eighth day after operation, ileus, gastric retention and marked prostration developed. In spite of energetic measures the patient died four days later; death was preceded by dementia and coma.

Necropsy revealed a healthy operative field, the evidence of old, healed tuberculosis of the upper lobe of the right lung, pulmonary embolism with infarction of the lower lobe of the right lung and pleuritis. Also, there were mucopurulent enteritis and healed, ulcerative sigmoiditis and proctitis.

Comment.—In this case, with reliable evidence of pellagra, at least from a dermatologic standpoint, there was associated gastric hyperacidity. The dermatitis had retrogressed considerably within a week after the operation. It is probable that our endeavor to supply a diet high in meat protein and vitamins precipitated the gastric retention. At no time prior to death was there evidence of a sudden onset of acute dyspnea and cyanosis characteristic of pulmonary embolism. Although there was no history of sore mouth, and although the diarrhea had preceded the dermatitis by a considerable period and did not persist, the disclosures at necropsy would support rather than cause rejection of the diagnosis of pellagra. Denton maintained that the colon is the site of pathologic changes in all cases of pellagra and that diarrhea seems to follow chiefly on changes in the sigmoid and rectum. In this case, it is probable that the changes found may have had a tuberculous origin in view of the history of the case. The grave risk of operation on patients with pellagra and the futility and harmfulness even of an early and adequate regimen, pushed too zealously perhaps, are well exemplified in this case.

CASE 2.—A man, aged 63, gave a history of progressively severe gastric disturbances of one year's duration, associated with loss of weight, appetite, strength and color, and aggravation of constipation of long standing. He had been on a milk diet exclusively for six months. Only rarely since the onset of his illness had he attempted to eat solid food, and invariably he had only chewed and expectorated it because it was distasteful. Two months prior to admission, "sunburn" developed on the backs of both hands and lesions appeared on the cheeks and nose. A local physician had prescribed ointment for the former.

On examination the patient was found to be emaciated and dehydrated, and 43 pounds (19.5 Kg.) under his usual weight. He was anemic. The concentration of hemoglobin was 55 per cent, and the erythrocytes numbered 3,740,000 per cubic millimeter of blood. A firm, somewhat flattened, slightly mobile, nonsensitive mass was palpated in the upper part of the epigastrium. Laboratory investigations revealed achlorhydria and gastric retention, a filling defect in the pars pylorica characteristic of medullary carcinoma and a large residue of barium after six hours. The cutaneous lesions, symmetric and sharply demarcated, were considered typically pellagrous.

After five days' preparation, partial gastrectomy was performed. A carcinoma measuring 10 by 8 by 2 cm. was removed, including the involved regional lymph nodes. For four days, the postoperative convalescence was uneventful and the cutaneous lesions improved noticeably. Then diarrhea appeared and persisted, accompanied by dementia, on and after the fifth day. In spite of energetic measures, circulatory collapse developed; the patient became maniacal and died on the seventh day following the operation. Necropsy disclosed the operative field to be healthy. Acute enteritis and degenerative changes were present in the posterior columns of the spinal cord.

CASE 3.—A man, aged 44, had had periodic attacks of indigestion simulating duodenal ulcer for more than seven years. For three months prior to admission to the clinic, the symptoms had become more marked. The usual measures for relief from pain and discomfort, by giving food and alkalis, were progressively less effectual, and there were periods of nausea and vomiting of unduly retained food, progressive loss of weight and strength and habitual constipation. Six weeks prior to admission, the patient experienced severe diarrhea, which lasted two weeks. Also, there were stomatitis and lesions involving the dorsum of the hands and wrists, presenting the characteristic gloved appearance. Nervous irritability, depression, insomnia, uncertain gait attributed to marked weakness, emaciation and anemia were also present.

Examination of the gastric contents revealed the absence of free hydrochloric acid in all of the specimens removed by the fractional method, and evidence of motor impairment of low grade. Roentgenoscopic examination gave evidence of a small filling defect on the lesser curvature and pars media, characteristic of carcinoma. A semisolid diet, totaling 2,200 calories daily, including 5 Gm. of Harris' brewers' yeast, caused marked improvement, especially in the diarrhea and the cutaneous manifestations. Operation was deferred, and at the time of the patient's departure the cutaneous lesions had entirely disappeared.

The patient was admitted later to a hospital in another state because of increasing gastric discomfort and retention, undoubtedly the result of a malignant lesion of recent origin in the pyloric antrum.

Comment.—The chief features in this case were evidence of pyloric obstruction due to a malignant lesion, first regarded as benign; a history of dietetic inadequacy; pellagra characterized by diarrhea and

lesions of the mouth, hands and wrists; nervous and mental disturbances; cachexia, and anemia.

CASE 4.—A woman, aged 58, who had borne twelve children, first consulted us in 1913, because of pelvic and digestive disturbances of several years' duration. The digestive symptoms were suggestive of duodenal ulcer.

Examination revealed deformity of the duodenal cap. Gastro-enterostomy had been done elsewhere in 1922. For nine months prior to the patient's second admission to the clinic, in March, 1926, she had a recurrence of her original ulcer-like symptoms, in addition to painful epigastric seizures, with wide radiation and associated chills, nausea, vomiting, residual soreness and loss of weight and strength. She was emaciated and anemic (hemoglobin 58 per cent and erythrocytes 3,590,000); there were tenderness, protective spasm throughout the epigastrium and right upper quadrant of the abdomen and possibly a mass in the latter region. The evidence suggested a poorly functioning gastro-enterostomy stoma requiring surgical intervention.

At operation, the stoma was found to be small, almost completely obstructed and situated within about 3 cm. of the pylorus. There was a mass in the pylorus, regarded as the result of an old inflammatory process. The old gastrojejunal anastomosis was disconnected and a new one was made in the usual situation. As the jejunum was small and considerably traumatized, the surgeon, at the completion of the operation, believed that extensive resection would have given better ultimate results.

The postoperative course was characterized by the onset of stomatitis and lesions on the dorsums of both hands and wrists. Three months later characteristic dermatitis of glovelike distribution was found. The patient had been living on cereals and bread only, for about a year. These lesions disappeared on treatment, but the stomatitis and tendency to vomit persisted. A third examination, two months later, revealed a serious condition, with evidence of marked involvement of the nervous system, depression, gastric motor disturbances and alkalemia. In spite of energetic treatment the patient failed rapidly, and death was preceded by ileus, persistent vomiting, cyanosis and collapse. Permission for necropsy was refused.

CASE 5.—A man, aged 44, entered the clinic in October, 1924. He gave a history of having had gastric disturbances intermittently for fifteen years. Gastro-enterostomy, performed elsewhere nine months prior to admission in the clinic, had given relief for a month. A second operation, performed by another surgeon seven months prior to admission, caused subsidence of the gastric pain, but vomiting, of the kind seen in retention, and diarrhea ensued. Simultaneous with the onset of the diarrhea, a month prior to admission, the patient noted dermatitis on the backs of the hands and forearms, glossitis and marked loss of weight.

Examination revealed pellagrous lesions on both hands and wrists, the forehead and the nose. There was achlorhydria and roentgenologic evidence of two gastro-enterostomy openings, as well as deformity of the duodenal cap. *Trichomonas hominis* and *Endameba histolytica* were present in the feces. A culture of the feces for *Aspergillus* gave negative results.

Operation disclosed extensive perigastric adhesions involving the upper part of the intestinal tract. There were two gastro-enterostomy openings, with a sharp kink of the intestine between them. Both anastomoses were disconnected, and pylorectomy was performed because of the presence of a hard, indurated, duodenal ulcer. Temporary jejunostomy was made just below the lower opening in the

jejunum, which had been closed, and this permitted feeding by tube. The jejunostomy wound closed spontaneously when the tube was removed three weeks after operation. Delirium and dementia developed on the third day after operation and lasted a fortnight. Institution of a proper diet, including fruit juices, brewers' yeast and puréed green vegetables, was followed by rapid recovery from the mental disturbances and gradual disappearance of the cutaneous lesions and diarrhea. The patient returned for examination a year later and was found to be in perfect health.

CASE 6.—A man, aged 62, entered the clinic on June 14, 1926. He gave a history of having had gastric disturbances for five years, characterized by epigastric discomfort, pyrosis, intolerance for acidulous fruits and constipation. For a year he had had a sense of impaired gastric motility with regurgitation of food which had necessitated the restriction of his diet to soups and liquids for six months prior to admission. He had lost weight.

Examination disclosed moderate emaciation, secondary anemia, achlorhydria and evidence of gastric retention. Considerable fresh and altered blood was found in the gastric content. There was roentgenologic evidence of an obstructing lesion at the pylorus. Bilateral, symmetric lesions were noted on the dorsums of the hands; these lesions had been present for a month and were highly suggestive of pellagra.

At operation, two small ulcers were excised from the lesser curvature and pars media of the stomach. These were found to be benign on microscopic examination, although carcinoma was suspected because of anacidity and retention. The gallbladder was distended, and there was evidence of marked pericholecystitis. The gallbladder was removed because it was causing compression and twisting of the first portion of the duodenum and was probably the causative factor in the gastric retention.

Convalescence was uneventful. After a period of improvement, the patient again suffered a relapse, complaining of asthenia, epigastric soreness, anemia, inability to gain weight, migrating arthralgia and poor circulation. Five months later, analysis of the gastric content revealed anacidity, but there was no evidence of a lesion on roentgenologic examination. Death occurred ten months after operation. Necropsy was not obtained. The patient's wife reported that the deceased "just continued to dry up and finally starved to death." The presence of cutaneous lesions was not mentioned.

CASE 7.—A married woman, aged 46, came under our observation on June 17, 1929. She gave a history of two attacks of illness, following dietary indiscretions, in February and May, 1929, when she passed tarry stools, associated with considerable prostration. On the last occasion transfusion of 1 liter of blood had been necessary. Anemia had been present since the last hemorrhage.

Examination revealed moderate secondary anemia, the presence of free hydrochloric acid in the gastric content and roentgenologic evidence of an ulcerating lesion high in the cardiac end of the stomach, which, because of its size, was thought to be malignant.

On June 22, operation disclosed a freely movable ulcerated lesion in the fudus of the stomach, surrounded by an inflammatory mass about 7 cm. in diameter. Jejunostomy after the method of Witzel was made, and jejunal feedings were instituted.

Diarrhea appeared a month prior to the patient's second admission, in September. This was followed, two weeks later, by acute proctitis, acute stomatitis and glossitis and roughening and fissuring of the knuckles of both hands. The cuta-

neous lesions were sharply delineated. The pellagrous nature of the lesions was verified, and they were attributed to inadequate jejunal feedings, owing to a misrepresentation of instructions on the part of the patient. The concentration of hemoglobin was 67 per cent, and the erythrocytes numbered 4,710,000. The concentration of hydrochloric acid in the gastric content was somewhat reduced. The patient was given a diet high in vitamin G, including scraped beef, fresh fruit juices, dried brewers' yeast and salmon. The daily intake of food was equivalent to 2,400 calories. The patient's weight was maintained on this regimen. There was marked and rapid improvement in the lesions of the skin and mucous membranes. The size of the gastric lesion remained unchanged.

In November, a third examination revealed an increase in weight of 16 pounds (7.3 Kg.). The anemia persisted, and, owing to the local discomfort caused by the jejunal tube, it was removed. Meals with a high content of vitamin and iron were resumed without incident. The lesion in the stomach was reduced in size, the stomach was more flexible in the region of the lesion and the patient was in much better spirits. In February, 1930, examination showed that the patient had regained her normal weight, the anemia had disappeared, the acidity of the gastric content was normal, there were no subjective complaints and the roentgenologic examination revealed persistence of a niche, reduced somewhat further in size.

Comment.—In this case, there was a deficiency disease, with cutaneous lesions of a pellagrous nature, as the result of postoperative jejunal feedings in the presence of a large lesion situated high in the stomach. The lesion may have been benign or malignant; it was not feasible to remove it at the time of operation.

Case 8.—A woman, aged 45, entered the clinic in October, 1927, complaining of gastric disturbances of about ten years' duration. Her diet had been markedly restricted for a long time, and at times she had been unable to retain even water. The condition had been diagnosed previously as hour-glass stomach on the basis of an apparent syphilitic gumma. Antisyphilitic treatment was instituted, but in spite of improvement, the patient eliminated vegetables, fruit and meat from her diet to a large extent.

Examination revealed an anemic, markedly undernourished woman. There were achlorhydria and a filling defect rather characteristic of syphilis in the pyloric antrum, and the Wassermann reaction of the blood was strongly positive. There was evidence of "fading" pellagrous dermatitis on the dorsa of both hands. Marked symptomatic improvement, barring a temporary setback caused by exfoliative dermatitis of low grade, followed antisyphilitic treatment and a suitable diet.

Comment.—In our opinion a patient with advanced gastric syphilis is an excellent candidate for grave nutritional disturbances and especially for pellagra. Frequently there is marked contracture of the stomach with corresponding reduction in its capacity, anacidity, anorexia, inability as the result of coincident involvement of the liver and cachexia. It is to partake of food in adequate amounts, grave metabolic disturbances possible that evidences of pellagra frequently have been overlooked in such persons.

Case 9.—A married woman, aged 33, entered the clinic on March 8, 1922. There was a background of a psychoneurotic family history. The patient was

nervous and asthenic, and her married life was unhappy. She gave a history of severe hematemesis and melena eight years prior to admission. This had been attributed to gastric ulcer by a local physician. For six years prior to admission she had given evidence of mental derangement, apparently of the manic-depressive type. Five months prior to coming to the clinic she attempted to commit suicide by drinking strong lye. This was followed by marked progressive obstruction of the esophagus, which necessitated liquid nourishment given in small amounts. Owing to her depression she often refused nourishment in any form, and this resulted in marked loss of weight and strength. Three previous, unsuccessful attempts at dilatation of the esophagus had been made. Three weeks prior to admission, there had been an onset of diarrhea, stomatitis, glossitis and symmetric dermatitis on the backs of both hands, extending to the wrists, with sharp demarcation.

On examination the patient was found to be apathetic, prostrated and emaciated. Introduction of a bougie revealed a rather dense stricture of the esophagus; the first obstruction was 30 cm. below the incisors and the second, 5 cm. lower. These strictures were gradually dilated so that food could be swallowed freely. The diarrhea persisted, bronchopneumonia developed two weeks after admission, and death occurred five days later. Necropsy revealed chronic inflammation of the esophagus, with constricting scars and multiple diverticular formations, chronic pyloric gastritis with an old healed ulcer, advanced emaciation with terminal bronchopneumonia and pellagrous lesions on the skin of the hands and wrists.

Comment.—It is our opinion that this is the only instance in the available literature of pellagra secondary to benign stricture of the esophagus.

Case 10.—A man, aged 45, was admitted to the clinic in November, 1923. He had had gastric disturbances over a period of twenty years which were suggestive of duodenal ulcer, and for which the gallbladder and appendix had been removed elsewhere in 1919, without relief from symptoms. Six months later, gastroenterostomy had been performed by the same surgeon. The original symptoms still persisted, and the constipation, which had been present before the operation, was replaced by from eight to fifteen loose bowel movements a day. There was also considerable loss of weight and strength, followed by depression and nervousness. Five months prior to admission, the following lesions appeared: symmetric dermatitis, glovelike in distribution, with marked pigmentation; a circumoral eruption having a brownish-black, maculopapular, pigmented appearance; marked erythema of the gums and edges of the tongue and bilateral circumscribed areas of suprapatellar infiltration. Dermatologic examination confirmed the belief that the lesions were pellagrous. The patient had refrained from the use of milk, cream and fruits for years, and owing to loss of appetite and to discomfort after meals since the last operation, he had eaten little.

Laboratory investigations revealed achlorhydria. Roentgenologic studies of the stomach, duodenum and colon gave no evidence of gross disease, barring slight deformity and contraction of the region of the anastomosis in the stomach. On a diet high in vitamins and the intramuscular administration of sodium cacodylate, the cutaneous lesions disappeared within a month, and the diarrhea was markedly lessened. The epigastric discomfort persisted in variable degree.

The patient was examined again about four years later, chiefly because of depression, with the obsession of threatened mental disorders and the fear of doing violence to his family. A neuropsychiatric survey did not result in a

diagnosis of actual psychosis, and there was no tangible evidence of recurring pellagra. Amebas in both vegetative and encysted forms, resembling *Endameba histolytica*, and other protozoa were found in the stool; acetarsone was prescribed. Administration of dilute hydrochloric acid in orangeade and institution of a diet with low residue caused prompt and marked improvement.

Case 11.—A man, aged 48, was admitted to the clinic in August, 1924. He gave a history of gastric disturbances, suggestive of a chronic gastric ulcer, that had been present for twenty-three years. Gastro-enterostomy had been performed, and the appendix had been removed in 1914. This was followed for a year by daily vomiting of food and of a profuse quantity of greenish, sour fluid. His condition gradually improved, but gaseous distress and constipation persisted. There was no marked dietetic imbalance, although he "watched his diet carefully to avoid stomach trouble." In the spring of 1923, and also in 1924, symmetric, erythematous areas appeared on the dorsa of both hands extending to the wrists; the condition was not relieved by wearing gloves. These lesions at first were maculopapular, but they shortly became vesicular. Residual, brownish pigmentation and lichenification were noted at the borders of the patches. Three months prior to admission, paresthesia of the upper and lower extremities appeared and persisted. In addition, weakness and depression, later associated with vertigo and syncope for a short period, and disturbances of speech and respiration were noted.

Examination revealed some malnutrition, moderate anemia, septic tonsils, prolapsed, tender and bleeding hemorrhoids and achlorhydria. There was no roentgenologic evidence of gastric ulcer or duodenal deformity, and the stomach appeared to be functioning normally. Ligation and excision of the internal hemorrhoids two months after admission were followed by satisfactory convalescence. In the following spring, the patient's local physician treated him for a third vernal attack of "pellagrous dermatitis" without associated diarrhea, stomatitis or mental disturbances. To successive business reverses were also attributed the recurrence of gastric disturbances and asthma. The dermatitis responded promptly to a diet high in vitamins, in which fresh meat, fresh fruits, yeast and fresh vegetables figured prominently.

Case 12.—A man, aged 55, had been losing weight and strength for eighteen months prior to admission. For six months he had been unable to work, and during that time he had lost the difference between 218 (97.7 Kg.) and 135 pounds (61.2 Kg.). For three months prior to admission he had complained of distress, usually in the region of the left hypochondrium, which came immediately after eating. Finally, the pain became more and more constant, but it was still aggravated by the taking of food. As a result, the patient had, for four or five weeks, limited his diet to oatmeal, a little milk and soup made of beans and potatoes. During this time there was persistent diarrhea. Shortly before he came to the clinic he noticed a cutaneous eruption.

Examination showed the patient to be emaciated and depressed. The tongue was reddened and glazed. There were some pulmonary emphysema, many large hemorrhoids and some edema of the legs. Typical acute lesions of pellagra involved both wrists, the face and the neck. A neurologic examination disclosed nothing abnormal. Roentgenologic examination gave evidence of a small filling defect in the descending colon. The urine contained some albumin and hyaline casts. The concentration of hemoglobin was 57 per cent, and the erythrocytes numbered 4,200,000. In spite of efforts made to give him more food, he failed rapidly and died ten days after admission. At necropsy the pathologist found

a carcinoma of the descending colon. The lesion had perforated into the pelvis of the left kidney. Fatty changes in the liver and evidence of old healed tuberculous pleuritis and lymphadenitis in the thorax were found.

CASE 13.—A woman, aged 21, was admitted to the clinic in September, 1927. There was definite clinical evidence of severe ulcerative colitis of ten months' duration, with marked anemia, complicated by erythema nodosum and acute polyarthritis in both knee joints. Hospitalization for these complications had been necessary at home prior to coming under our observation. After three months' treatment, the patient had improved somewhat and was dismissed. Owing to her failure to cooperate properly, she found it necessary to return to the clinic in January, 1928, with evidence of peripheral neuritis, apparent dementia, marked emaciation and weakness. In spite of energetic treatment in the hospital, the following signs developed: fever and marked contracture of both legs, progressive emaciation, severe stomatitis and marked psychosis and purposeless tremors involving the muscles of the face and arms. The condition of the bowels was satisfactory. Eight months after the original admission, lesions on the hands and wrists, characteristic of pellagra, were first noticed. These may have been present before in milder degree. On institution of proper dietetic measures, with adequate amounts of food containing vitamin G, mental improvement and a gain in weight were recorded. A month after the patient's return home her nurse reported marked general improvement.

Comment.—Barnes reported a case of fatal pellagra, developing in a patient with chronic ulcerative colitis, in which the pellagrous lesions were of a much more severe degree than those seen in this case. They involved the feet and face, in addition to the hands and wrists, and occurred while the patient was under dietetic treatment for colitis in the hospital.

SUMMARY

Pellagra developed in eight patients with obstructing benign lesions or dysfunction (late, after operation) of the upper part of the digestive tract, in two with obstructing carcinomatous lesions, in one with gastric syphilis and in two with lesions of the colon (one carcinomatous, one inflammatory). This secondary form of pellagra tends to support the theory that dietetic deficiency is the cause of the disease. In the cases reported, the clinical manifestations of the disease were not as marked as those of the active, endemic type of pellagra. Treatment may be ineffectual in cases with mechanical obstruction or in those with marked impairment of motility of the upper part of the digestive tract, until the mechanical condition is corrected. Surgical intervention is attended by high mortality. Case reports covering the essential clinical features are submitted.

II. THE GALACTOSE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE*

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In a previous article [1] dealing with the metabolism of galactose, we discussed the work of various investigators and detailed some of our own observations leading to the conclusion that galactose offers the best means of investigating the carbohydrate function of the liver. We do not consider it adequate as a routine test for liver function; on the contrary, its limitations are definite, and it is precisely these limitations that enable it to serve a special purpose, that of an aid in the differential diagnosis of jaundice.

The discovery of the glycogenic function of the liver in 1857 by Claude Bernard at once stimulated the interest of clinicians as well as physiologists and pathologists in the question of carbohydrate metabolism. This interest was soon manifest in an extensive literature, and the idea of utilizing the sugars for testing hepatic function was a natural outgrowth. Such attempts, however, resulted in divergent results, and, particularly during the last quarter of the nineteenth century, created a controversy between the German and French schools. The German school, notably Quincke,[2] von Noorden,[3] Kraus and Ludwig,[4] and Bloch,[5] was unable to demonstrate any marked or constant reduction of tolerance for sugar in hepatic disease; the French school, on the other

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1. Shay, H.; Schloss, E. M., and Bell, M.: The Metabolism of Galactose: Considerations Underlying the Use of Galactose in Liver Function Tests, Arch. Int. Med., to be published.

2. Quincke, H.: Symptomatische Glycosurie, Berl. klin. Wchnschr. **13**:529 and 547, 1876.

3. von Noorden, F.: Pathologie des Stoffwechsels, Berlin, August Hirschwald, 1893, p. 274.

4. Kraus, F., and Ludwig, H.: Klinische Beiträge zur alimentären Glycosurie, Wien. klin. Wchnschr. **4**:855, 1891.

5. Bloch, G.: Ueber alimentäre Glykosurie, Ztschr. f. klin. Med. **22**:525, 1893.

hand, including Achard and Castaigne,[6] Baylac,[7] and Bierens de Haan,[8] favored the sugars as test substances for hepatic function. Strauss[9] attempted to explain and partially reconcile these divergences on the basis of the various sugars and amounts of sugars used as test substances.

The extent and character of liver activity in carbohydrate metabolism may be briefly summarized as follows:

1. The conversion of monosaccharides (dextrose, levulose, galactose) brought to the liver cells by the blood, into glycogen, a polysaccharide closely related to starch
2. The temporary storage of glycogen, as such
3. The reconversion of glycogen into dextrose by liver enzymes, as need arises for sugar throughout the body
4. The vital character of this function

It is with this last mentioned character, only recently definitely established, that we are most concerned. As early as 1874, Bock and Hoffman[10] indicated the importance of the carbohydrate function of the liver. These investigators found a diminution of blood sugar after the liver had been removed or shunted from the circulation. Many observers have repeated these experiments, but it remained for the classic investigations of Mann and his co-workers[11] to establish the importance of this function of the liver. They found that immediately after the removal of the liver, the blood sugar decreases progressively; when it reaches a certain rather definite limit, of from 0.06 to 0.04 per cent, a characteristic group of symptoms appears, and, if allowed to continue, death soon ensues. Mann showed that these phenomena could be controlled by the injection of dextrose, and that the duration of the control, within certain limits, depended on the amount of dextrose administered. Mann[12] definitely stated that the removal of the liver completely severs a part of the vital normal process of carbohydrate metabolism.

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6. Achard, C., and Castaigne, J.: L'épreuve de la glycosurie alimentaire et ses causes d'erreur, Arch. gén. de méd. **1**:27, 1898.

7. Baylac, J.: De la valeur de la glycosurie alimentaire dans le diagnostic de l'insuffisance hépatique, Compt. rend. Soc. de biol. **4**:1065, 1897.

8. Bierens de Haan, J. C. J.: Ueber alimentäre Glykosurie bei Leberkranken, Arch. f. Verdauungskr. **4**:4, 1898.

9. Strauss, H.: Zur Funktionsprüfung der Leber, Deutsche med. Wchnschr. **27**:757, 1901.

10. Bock, C., and Hoffman, F. A.: Experimental Studien über Diabetes, Berlin, H. E. Oliven, 1874.

11. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver. II. The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73 (July) 1922.

12. Mann, F. C.: Modified Physiologic Processes Following Total Removal of the Liver, J. A. M. A. **85**:1472 (Nov. 7) 1925.

It is readily seen from a brief review of the literature that investigations of the use of the sugars in testing liver function were productive of widely variant results and equally divergent interpretations. However, the fact seems to have been completely overlooked that nature, in providing for so vital a faculty, has characteristically created an organ with adequate reserve, such a reserve as may be demonstrated in the kidney, the lung, etc. Then, too, little consideration was given the remarkable power of regeneration of the liver cells, as a result of which, in chronic damage of these cells, one may see cellular regeneration and degeneration proceeding simultaneously. It is because of these two properties, adequate reserve and a strong tendency to regeneration, that in cases of slow or local disease of liver cells there is sufficient actively functioning liver tissue to maintain the carbohydrate mechanism. From these considerations, it becomes obvious that one should expect changes in the carbohydrate function of the liver only when all or nearly all the liver cells are damaged more or less acutely or when chronic damage of these cells has progressed extensively and regeneration has failed. This contention is strengthened by the experiments of Roubitschek,[13] who found marked galactosuria in animals poisoned with phosphorus; not only was the acute diffuse damage of the liver cells, reflected in this galactosuria, but in those cases in which, despite additional poisoning with phosphorus, there was a recession of the galactosuria, postmortem examination revealed regeneration of the liver cells. These facts, then, of adequate hepatic reserve and ready hepatic regeneration aid in the clarification of the variable results that have attended the efforts to utilize the carbohydrate function as a routine test of liver function. The very limitations of this type of test, however, form the basis for its use in the differential diagnosis of jaundice.

As we have previously indicated, a derangement of the carbohydrate function of the liver might be expected in acute or subacute diffuse damage of the liver cells; this type of disease is usually accompanied by jaundice. Such a derangement of function might, then, be used in identifying those cases of jaundice due to acute or subacute diffuse damage of the liver cells, in other words, the toxic and infectious types of jaundice. It is this group that has clinically presented the greatest difficulty of early recognition. In these cases, none of our laboratory procedures offer much aid in diagnosis. It was hoped, at one time, that the qualitative van den Bergh reaction would serve to identify and differentiate the various types of jaundice; this very group of toxic and infectious

13. Roubitschek, R.: Alimentäre Galaktosurie bei experimenteller Phosphorvergiftung, Deutsches Arch. f. klin. Med. **108**:225, 1912.

cases proved to be its Waterloo. The need for a means of identifying this type is apparent. We shall attempt to demonstrate in this report of our preliminary series that the carbohydrate function test serves to identify this group and to differentiate it from the obstructive and hemolytic types of jaundice. For this purpose, the galactose tolerance test has been used. It was chosen on the basis of the superiority of galactose over levulose in testing liver function. The interpretation has been based on the urinary output of galactose since, for the present at least, this appears to serve as the best measure of the utilization of galactose by the liver.[1]

TECHNIC OF GALACTOSE TOLERANCE TEST

This test was introduced by Richard Bauer, of Vienna, in 1906.[14] The following is the method as we have employed it at the Jewish Hospital in Philadelphia for the past two years:

The test is preceded by a twelve hour fast, and the patient receives no breakfast. On the morning of the test, the patient voids; this specimen is examined qualitatively for sugar. Pure galactose, exactly 40 Gm., dissolved in about 500 cc. of water, usually flavored with a few drops of lemon juice, is administered orally. The patient voids completely at the next successive five hours, and the specimens are collected in toto and labeled. Since Cori[15] has shown that the rate of absorption of the sugar is independent of both the absolute amount and the concentration of the sugar in the intestine, the patient may have as much water as desired during the test, but nothing else. If specimens are not obtainable on the hour, they are secured as close as possible to the hour periods. The important point is that all urine voided during the five hour period following the ingestion of the galactose is to be collected.

Determination of Galactose Excreted.—1. In Nondiabetic Persons: Each of the specimens obtained at the hourly period is tested qualitatively for sugar. The positive specimens are then mixed, the total quantity measured, and a quantitative determination of sugar is carried out by the Benedict method. The total amount of galactose excreted in the urine is then calculated.

A word may not be amiss here as to whether the sugar excreted in the urine after the ingestion of galactose is actually galactose. The resistance of the sugar excreted to fermentation by yeast, its convertibility to mucic acid (Bauer,[16] MacLean and de Wesselow[17]) and its greater rotating effect on polarized light have been factors in its identification.

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14. Bauer, R.: Ueber die Assimilation von Galaktose und Milchzucker beim Gesunden und Kranken, Wien. med. Wchnschr. **56**:20, 1906.

15. Cori, C. F.: The Fate of Sugar in the Animal Body. The Rate of Absorption of Hexoses and Pentoses from the Intestinal Tract, J. Biol. Chem. **66**:691, 1925.

16. Bauer, R.: Weitere Untersuchungen ueber alimentäre Galaktosurie, Wien. med. Wchnschr. **56**:2538, 1906.

17. MacLean, H., and de Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med. **14**:103, 1921.

In one study, its actual isolation from the urine (Halberkann and Kähler[18]), with a comparison of the sugar obtained with pure galactose, including the melting point, formation of osazone and the conversion of mucic acid, has established the identity of the excreted sugar as galactose.

2. In Diabetic Persons: It is obvious that the question of the utilizability of this test in diabetic persons should arise. Bauer,[16] in one of his earlier papers, doubts its efficiency in such cases. Our[1] studies, however, indicate that the utilization of galactose by the liver is independent of the condition of the pancreas. By applying the method suggested by Somogyi[19] for the separation of galactose from dextrose in the blood, we have been able to do so satisfactorily in the urine. This method is dependent on the rapid fermentation, by a yeast suspension, of dextrose, as compared to that of galactose. Care must be exercised in the preparation of the yeast suspension, as commercial yeast is always contaminated with adhering particles of wort which contain nonfermentable reducing substances. A weighed amount of fresh commercial yeast is suspended in from five to ten parts of water; this is centrifugated, and the water decanted. This operation is repeated until the supernatant liquid is practically clear and colorless, and fails to show the presence of any reducing substances when tested with Fehling's solution. The yeast is then ready for use, and a 10 per cent suspension is prepared.

In dealing with this test in a diabetic person, the quantitative determination of sugar is carried out in the usual manner as described, and the total amount of sugar is estimated. The urine and yeast suspension are then mixed in the proportion suggested by Somogyi for the blood; namely, 1 part of urine and 7 parts of the 10 per cent yeast suspension. (To correct as nearly as possible for the actual volume of yeast in the suspension, an allowance of 10 per cent of the suspension is made; e. g., if 1 cc. of urine is used, 7.7 cc. of the 10 per cent suspension of yeast is added, allowing the 0.7 cc. for the volume of yeast cells in the suspension.) We have experimented with smaller proportions of yeast, but have not obtained satisfactory fermentation. The mixture is then incubated for forty-five minutes. By this method, we have been able to obtain a complete destruction of the dextrose in solution, while the loss of galactose has not exceeded 10 per cent. Therefore, for all practical purposes, the determination of the sugar remaining after such fermentation, represents the galactose excreted during the tolerance test. The difference between this determination and the reading before fermentation represents the amount of dextrose present. These results of fermentation are practically identical with those obtained by Corley,[20] using the Shaffer-Hartmann micromethod for determination.

CLINICAL APPLICATION OF THE GALACTOSE TOLERANCE TEST

In a previous contribution,[1] we presented evidence that the normal tolerance for galactose ranges between 37 and 40 Gm. The normal person, then, in whom there is no disturbance of the carbohydrate function

18. Halberkann, J., and Kähler, H.: Beiträge zur Leberfunktionsprüfung. Isolierung und Identifizierung der mit dem Harn angeschiedenen d-Galaktose, Ztschr. f. phys. Chem. **154**:34, 1926.

19. Somogyi, M.: Reducing Non-Sugars and True Sugar in Human Blood, J. Biol. Chem. **75**:33, 1927.

20. Corley, R. C.: Factors in the Metabolism of Lactose. The Disposal of Intravenously Administered Galactose in the Rabbit, J. Biol. Chem. **74**:1, 1927.

of the liver, may excrete from 0.0 to 3.0 Gm. of galactose in the five hour period following the ingestion of 40.0 Gm. of that sugar. In cases of jaundice due to factors other than acute diffuse damage of the liver cells, sufficient active liver tissue is present to carry on carbohydrate metabolism. Thus, obstructive or hemolytic jaundice gives readings within the normal range. On the other hand, in jaundice accompanying acute diffuse damage of the liver cells, the carbohydrate function is impaired, and the liver, unable to utilize the normal quantity of galactose, allows a quantity of this sugar, larger than normal, to pass and reach the general circulation. In the absence of a kidney threshold for galactose,[1] this excess appears in the urine. Hence, in jaundice with sufficient damage of liver cells, quantities of galactose greater than 3 Gm. appear in the urine in the five hours following the ingestion of 40.0 Gm. of this sugar.

A review of the literature on the reported cases studied with the galactose tolerance test reveals many points of interest. While it is, we believe, beyond the province of this paper to discuss these cases in detail, certain observations of such a review warrant discussion. Bauer in his earlier work [16] thought that he had found a test for cirrhosis of the liver. It was not until two years after his first publication that he [21] reported the finding of an alimentary galactosuria in catarrhal jaundice. He reported at this time a series of ten cases of catarrhal jaundice in which the alimentary galactosuria became evident early in the illness, increased somewhat during its course, and decreased as the jaundice disappeared. We have noted practically identical observations in the present series of cases.

Considerable confusion arises in reviewing the literature, because of the different values for the normal standards that various authors have adopted for the test. Neugebauer [22] and Maliwa [23] considered as pathologic an output of over 0.6 Gm. after the ingestion of 40.0 Gm. of galactose. Reiss and Jehn [24] and Wagner [25] permitted an output of 2.0 Gm. under the same conditions to be accepted as normal. Most investiga-

21. Bauer, R.: Ueber alimentäre Galaktosurie bei Ikterus, Deutsche med. Wchnschr. **34**:1505, 1908.

22. Neugebauer, H.: Zur Pathogenese des Icterus catarrhalis, Wien. klin. Wchnschr. **25**:514, 1912.

23. Maliwa, E.: Bemerkungen zur Galaktose Intolerans, Med. Klin. **18**:762, 1922.

24. Reiss, E., and Jehn, W.: Alimentäre Galaktosurie bei Leberkrankheiten, Arch. f. klin. Med. **108**:187, 1912.

25. Wagner, F.: Klinische Untersuchungen ueber die Bedeutung der verschiedenen Zuckerproben für die Beurteilung der Leberfunktion, Ztschr. f. klin. Med. **80**:174, 1914.

tors, including ourselves, have followed Bauer, who considered outputs of 3.0 Gm. and more as indicative of impaired hepatic tolerance.

Wörner,[26] up to 1919, had collected from various authors 165 cases of catarrhal jaundice in which the galactose tolerance test had been performed. Of these, 133, or 80.5 per cent had shown a urinary output greater than 3.0 Gm. during the test. In 132 collected cases of icterus due to tumors and gallstones, 9, or 6.8 per cent gave readings above 3 Gm. We quote the preceeding figures, largely to point out that we do not believe that they represent a fair estimate of the test, in spite of the favorable appearance of the percentages. The element of chance works against the test in both groups of cases. Mild cases of catarrhal jaundice are not infrequently encountered; it has been our experience with this type that the carbohydrate function of the liver is comparatively slightly altered and tends to recover rapidly. In such cases, if the test happens to be delayed a few days, an apparently normal result may be obtained. Cases of chronic damage of the liver cells (tumor, cirrhosis, etc.), it must be remembered, can also reach the state in which the carbohydrate function of the liver may show impairment. The report of Reiss and Jehn [24] illustrated such an instance clearly. They cited a case of cirrhosis of the liver in which they obtained an output of 3.9 Gm. during the test. Studying the clinical notes accompanying this case, we find recorded a mild icterus of the skin and sclera, and intermittent fever. Only a few days after the galactose reading of 3.9 Gm. was obtained, autopsy showed a liver that grossly was entirely devoid of normal structure and microscopically presented a severe cirrhosis with areas of necrosis of the liver tissue. The point that we desire to make becomes obvious—that under any condition in which the liver reserve for carbohydrate function is destroyed there will be an abnormal galactose tolerance. It also becomes apparent that in such a group of cases as is represented by the above mentioned instance, no functional tests are necessary to help make the diagnosis. Another point worthy of mention at this time is that we must not overlook the fact that a so-called "catarrhal jaundice" may complicate the courses of many cases of chronic damage of the liver cells. We experienced such an instance in a case of cirrhosis in which a high galactose output was given during the jaundice but which returned to normal limits as the jaundice subsided.

All of the various conditions in which a high galactose output is reported fall in the group in which diffuse damage to the liver cells of an

26. Wörner, H.: Die praktische Bedeutung der Galaktoseprobe, Med. Klin. **15**:1142, 1919.

TABLE 1.—*Results of Galactose Tolerance Tests in Toxic and Hemolytic Jaundice*

Patient	Age	Diagnosis	Basis for Diagnosis	Type of Jaundice	Duration of Jaundice	van den Bergh Reaction		Bromsulphalein		Galactose Tolerance Test, Gm.
						Qualitative	Quantitative	Dose in Mg. per Kg.	Retention, per Cent	
1	8	Catarrhal jaundice	Clinical	Toxic	7 days	Biphasic	6.9	5	30	4.56
2	11	Catarrhal jaundice	Clinical	Toxic	7 days	Delayed direct	14.4	5	100	5.37
3	18	Catarrhal jaundice	Clinical	Toxic	11 days	Delayed direct	13.4	5	40	10.75
4	18	Catarrhal jaundice	Clinical	Toxic	27 days	Delayed direct	9.3	5	100	3.50
5	9	Catarrhal jaundice	Clinical	Toxic	13 days	Delayed direct	1.3	2	0	3.30
6	53	Catarrhal jaundice	Clinical	Toxic	15 days	Delayed indirect	12.8	2	100	5.50
7	53	Catarrhal jaundice	Clinical	Toxic	37 days	Biphasic	0.7	2	60	3.80
8	9	Catarrhal jaundice	Clinical	Toxic	12 days	Negative	1.9	5	0	5.18
9	31	Lung abscess with toxic hepatitis	Clinical	Toxic	2 days	Negative	4.5	..	...	4.60
10	9	Catarrhal jaundice	Clinical	Toxic	2 days	Biphasic	9.6	..	...	11.30
11	9	Catarrhal jaundice	Clinical	Toxic	Jaundice gone	.....	....	..	...	9.00
12	10	Catarrhal jaundice	Clinical	Toxic	?	Negative	1.6	5	5	3.60
13	12	Catarrhal jaundice	Clinical	Toxic	2 days	Delayed indirect	10.6	..	...	5.05
14	6	Catarrhal jaundice	Clinical	Toxic	7 days	Delayed indirect	4.0	..	...	6.31
15	6	Catarrhal jaundice	Clinical	Toxic	3 days	.....	....	..	...	3.65
16	6	Catarrhal jaundice	Clinical	Toxic	?	Delayed direct	5.2	..	...	3.02
17	19	Catarrhal jaundice	Operation	Toxic	9 weeks	Biphasic	16.3	..	...	3.48
									Average	5.41
1	26	Chronic hemolytic jaundice	Clinical	Hemolytic	Several years	Negative	4.6	..	...	0.00
2	5	von Jaksch's anemia	Clinical	Hemolytic	?	Negative	3.2	..	...	0.50
3	6	Chronic hemolytic jaundice	Clinical	Hemolytic	6 years	Negative	3.5	..	...	0.50
4	63	Pernicious anemia	Clinical	Hemolytic	?	Negative	4.6	..	...	0.39
									Average	0.43

TABLE 2.—*Results of Galactose Tolerance Test in Series of Patients with Obstructive Jaundice*

Patient	Age	Diagnosis	Basis for Diagnosis	Type of Jaundice	Duration of Jaundice	van den Bergh Reaction		Bromsulphalein		Galactose Tolerance Test, Gm.
						Qualitative	Quantitative	Dose in Mg. per Kg.	Retention, per Cent	
1	50	Carcinoma of head of pancreas	Operation	Obstructive	5 months	Delayed indirect	19.2	2	80	1.1
2	35	Cholelithiasis	Operation	Obstructive	6 days	Delayed indirect	6.2	..	...	0.0
3	63	Carcinoma of liver	Operation	Obstructive	3 weeks	Delayed indirect	16.6	2	100	0.69
4	42	Common duct adhesions	Operation	Obstructive	4 months	Delayed indirect	19.5	2	85	0.50
5	55	Cholelithiasis	Operation	Obstructive	3 days	Delayed direct	3.6	..	...	0.13
6	49	Carcinoma of liver	Clinical	Obstructive	2 days	Delayed indirect	6.4	2	60	0.70
7	50	Cholelithiasis	Operation	Obstructive	11 days	Delayed indirect	15.0	..	...	0.00
8	64	Cholelithiasis	Necropsy	Obstructive	6 months	Delayed direct	11.7	..	...	1.50
9	54	Carcinoma of liver	Clinical	Obstructive	13 days	Delayed direct	4.1	5	35	0.00
10	59	Carcinoma of head of pancreas	Clinical	Obstructive	9 months	Delayed indirect	15.0	2	70	0.30
11	64	Cholelithiasis	Operation	Obstructive	2 months	Delayed indirect	33.5	2	55	2.20
12	55	Cholelithiasis	Operation	Obstructive	5 weeks	Delayed indirect	11.0	..	...	0.25
13	64	Cirrhosis of liver	Biopsy	Obstructive	15 days	Delayed indirect	28.0	2	45	0.98
14	32	Cholelithiasis	Operation	Obstructive	2 days	Delayed indirect	3.1	5	100	0.19
15	59	Carcinoma of pancreas	Operation	Obstructive	4 weeks	Delayed indirect	4.5	2	45	1.10
16	64	Carcinoma of liver	Operation	Obstructive	?	Delayed direct	2.5	5	80	0.00
17	51	Carcinoma of liver and stomach	Clinical	Obstructive	?	Delayed direct	6.6	5	60	1.20
18	72	Carcinoma of head of pancreas	Operation	Obstructive	5 months	Delayed indirect	39.0	2	50	0.00
									Average	0.60

acute nature has doubtlessly occurred. Catarrhal jaundice is most frequently reported, while arsphenamine jaundice, acute yellow atrophy, phosphorus poisoning, syphilitic hepatitis and jaundice associated with lead poisoning as well as with various acute infections make up the list of other types of cases in which this test has been found positive.

The appended tables of our series of cases are divided into hemolytic, toxic and obstructive jaundice. The column "duration of jaundice" indicates the duration of the jaundice at the time at which the galactose tolerance was obtained. The last column indicates the number of grams of galactose excreted during the five-hour test period. A glance at the average output of each of the groups of jaundice presented will justify much that has been stated in the foregoing paragraphs.

CONCLUSION

We believe that the galactose tolerance test offers a means of identifying early the group of toxic or infectious jaundice, a group of cases that often tax the diagnostic acumen of the keenest clinicians. In the preliminary presentation of the aforementioned group of thirty-nine cases of various types of jaundice, we feel that the results are sufficiently striking to warrant further and more general investigation.

SUMMARY

The observations in thirty-nine cases of jaundice have been presented. On the basis of the galactose tolerance test performed in each case, the presence or absence of acute or subacute diffuse damage of the liver cells has been determined, and wherever possible, confirmation of diagnosis has been made by operation, biopsy or autopsy. The basis for the use of a sugar tolerance test in differentiating these groups of cases of jaundice has been described; the differentiation is attributed to the diffuse destruction or derangement of the hepatic cells, with consequent disruption of the carbohydrate mechanism on the one hand and the survival of sufficient functioning tissue to maintain so vital a process on the other. The reasons for the choice of galactose as the test sugar have been discussed in a previous paper.[27] The technic of the galactose tolerance test as used in these investigations is given.

27. Shay, H.; Schloss, E. M., and Bell, M. A.: Metabolism of Galactose: I. Considerations Underlying the Use of Galactose in Tests of the Function of the Liver, Arch. Int. Med. **47**:391 (March) 1931.

IV. THE DIFFUSIBLE CALCIUM OF THE BLOOD STREAM IN TETANY*

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The reduction of calcium in the blood in infantile tetany and in tetany due to parathyroid deficiency has been well recognized since the classic work of McCallum and Voegtlin.[1] On the other hand, no significant alteration in the total amount of calcium in the serum has been found in tetany induced by hyperventilation or by an overdosage of bicarbonate.[2] The differences in the analytic observations of the chemical composition of the blood in tetany of diverse origin[3] led Grant and Goldman to conclude: "Tetany occurs under so many circumstances that it probably cannot be attributed to a single etiological factor." This, however, has not deterred many from attempting to establish a common disturbing factor as the cause of all forms of tetany. Two hypotheses have been proposed with respect to the etiologic factors responsible for tetany: 1. All forms of tetany are due to an alkaline shift in the acid-base balance. 2. A lowering of the calcium ion concentration is

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* This research is one of a series carried out jointly by the Department of Medicine and the Division of Biochemistry of the University of California Medical School, with the cooperation of Professors W. J. Kerr and Carl L. A. Schmidt.

1. McCallum, W. G., and Voegtlin, C.: On the Relation of the Parathyroid Gland to the Calcium Metabolism and to Tetany, J. Exper. Med. **11**:118, 1909.

2. Grant, S. B., and Goldman, A.: Tetany Following Forced Respiration in Man, Am. J. Physiol. **52**:209 (June) 1920.

3. Grant (footnote 2). McCallum, W. G., and others: Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31**:1 (Jan.) 1920. Harrop, G. A.: Production of Tetany by Intravenous Infusion of Sodium Bicarbonate, ibid. **30**:62 (March) 1919.

the cause of tetany in all cases. The results of experiments carried out by us and others do not bear out either of these hypotheses as the sole factor responsible for tetany, and we must concur with Grant and Goldman that tetany cannot be attributed to any single etiologic factor.

The experiments carried out by us support the view that infantile and parathyroprival tetany are associated with a lowering of the physiologically available calcium of the blood stream. In our experiments this is demonstrated by a decrease in the diffusible fraction of the serum calcium. In contradistinction, tetany due to hyperventilation and an overdosage of a bicarbonate are induced by an alkaline shift in the acid-base balance of the blood without an accompanying decrease in the physiologically available calcium. In fact, our experiments showed high levels for the diffusible calcium in this form of tetany.

INFANTILE AND PARATHYROID TETANY

In previous communications we pointed out that the accumulated data show that the calcium in the blood stream is present practically only in the plasma, and that there it exists in several forms that are measurable by analytic methods. These fractions are the diffusible calcium, or the fraction able to pass through a membrane impermeable to colloids, and the nondiffusible calcium, the fraction held back by a membrane impermeable to colloids. The diffusible fraction contains the ionic blood calcium and the nondiffusible calcium is in all probability combined with the plasma proteins in a nonionized compound. The amount of nondiffusible calcium, then, may vary with the changes in the plasma proteins.

The present methods of analysis of calcium, based mostly on the Kramer and Tisdall procedure,[4] determine the total amount of calcium in the blood serum and do not differentiate between the physiologic states of the various fractions. Fluctuations in the diffusible and nondiffusible calcium fractions can occur in such a manner that they are not revealed by the analysis of the total amount of calcium, and therein lies a probable explanation for the discrepancies between laboratory and clinical observations in numerous instances of juvenile and para-

[4] 4. Kramer, B., and Tisdall, F. F.: Clinical Method for Quantitative Determination of Calcium and Magnesium in Small Amounts of Serum and Plasma, Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, J. Biol. Chem. **56**:439 (June) 1923.

thyroid tetany. Thus Liu [5] found that tetany may exist when the total amount of calcium in the serum is as high as 9 mg. per hundred cubic centimeters, and latent tetany may be present even when the total amount of calcium in the serum is as high as 10.2 mg. per hundred cubic centimeters. Our observations in parathyroid infantile tetany (table 1) confirm those of Liu and show that manifest and latent tetany can be present when the values for calcium in the serum are within the normal limits of variation. Figures for the total amount of calcium in the serum lying within the normal limits of variation, when symptoms of tetany were present, have not been an uncommon observation at the University of California Hosiptal.

The ideal diagnostic method for tetany by chemical means would be a procedure for measuring the amount of physiologically available calcium that is effective in the maintenance of the normal neuromuscular irritability. But here one is confronted with the difficult problem of what constitutes the physiologically available calcium. The work of Loeb,[6] Ringer,[7] and others pointed to the ionic calcium in the blood as being the best measure of physiologically available calcium for the control of neuromuscular irritability. Attempts at the determination of the ionic blood calcium have been made,[8] but all such proposed methods in their present state are clinically impracticable. An analytic procedure

5. Liu, S. H.: Comparative Study of Effects of Various Treatments on Calcium and Phosphorus Metabolism in Tetany: Chronic Juvenile Tetany, J. Clin. Investigation **5**:259 (Feb.) 1928; Chronic Adult Idiopathic Tetany, ibid. **5**:277 (Feb.) 1928.

6. Loeb, J.: On Ion-Proteid Compounds and Their Rôle in the Mechanics of Life Phenomena; 1. The Poisonous Character of Pure NaCl Solution, Am. J. Physiol. **3**:327, 1900.; On an Apparently New Form of Muscular Irritability (Contact Irritability?) Produced by Solutions of Salts (Preferably Sodium Salts) Whose Anions Are Liable to Form Insoluble Calcium Compounds, ibid. **5**:362, 1901.

7. Ringer, S.: A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, J. Physiol. **4**:2, 1883.

8. Neuhausen, B. S., and Marshall, E. K., Jr.: Electrochemical Study of Condition of Several Electrolytes in Blood, J. Biol. Chem. **53**:365 (Aug.) 1922. Brinkman, R.: Einige Bemerkungen über die Bedeutung des Blutkalks, Biochem. Ztschr. **95**:101, 1919. Trendelenburg, P., and Goebel, W.: Tetanie nach Entfernung der Epithelkörperchen und Calcium Mangel im Blute, Arch. f. exper. Path. u. Pharmakol. **89**:171, 1921.

TABLE 1.—*Observations in Parathyroid Infantile Tetany*[*]

Name	Calcium, Mg. per 100 Cc.			Inorganic Phosphate, Mg. per 100 Cc.	Proteins, per Cent		
	Total	Diffusible	Nondiffusible		Albumin	Globulin	
I. F.	...	...	...	...	...	...	Twelve hours after convulsion; positive signs of tetany present
8/25/28	6.3	3.3	3.0				
9/ 1/28	8.9	3.0	5.9	...	...	...	Convulsion preceded the taking of sample; signs of tetany present
10/10/28	9.0	3.0	6.0	...	...	...	Convulsion; signs of tetany present; sample taken after convulsion
6/ 6/29	8.5	4.2	4.3	...	...	...	Under treatment; subjective irritability present; Chvostek sign doubtful; no outright signs of tetany present
K.							
9/28/29	4.0	...	...	...	...	...	Reported from a reliable clinical laboratory; convulsion at time sample taken
9/29/29	7.2	3.7	3.5	...	...	...	Parathyroid extract Collip, 10 units, with calcium lactate by mouth 24 hours before sample was taken; subjective symptoms present
10/ 1/29	6.8	4.0	2.8	...	...	...	Medication was discontinued; sample taken on appearance of first subjective symptoms, consisting of fullness in head and stiffness of the face
Baby W.							
	10.2	3.2 4.1	7.0	...	...	...	Six weeks old; pneumonia; convulsions; calcium chloride administered by intravenous route; dose 5 cc. of 5 per cent solution for 5 days; cod liver oil by mouth; convulsions ceased after therapy; none at time second sample taken
Z.							
	7.6	3.2	4.4	2.4	...	...	Osteomalacia; tetany; convulsion prior to taking of sample
Br.							
	9.3	3.7	5.6	...	...	...	Man, aged 36; palpitation; tachycardia, tremor of hands, mild signs of hyperthyroidism; positive Hoffman sign; operation; microscopic examination showed lugolized hyperplasia of the thyroid gland; sample taken before operation
S.[*]	...	...	...	...	...	...	Chvostek and Hoffman signs, positive; patient very nervous; no convulsions
4/ 5/30	7.1	3.8	3.3	5.2	4.5	2.5	
4/11/30	Viosterol 6 minimums per day by mouth						Patient showed subjective relief; Chvostek sign not obtained
4/17/30	8.9	4.5	4.4	4.5	4.2	2.6	Hoffman sign doubtful
4/17/30	Viosterol 45 minimums per day by mouth						
5/ 7/30	7.2	3.5	3.7	4.7	3.9	1.6	Relapse; very nervous, questionable convulsions
Baby L.	10.9	5.5	5.4	...	...	...	Petit mal; calcium chloride administered intravenously; cod liver oil by mouth; convulsions continued, consisting of slight stiffening of legs and twitchings of one corner of mouth
Be.	11.1	5.8	5.3	...	...	...	Isolated muscle cramps
Ma.	10.6	5.4	5.2	...	...	...	Hysteria; carpopedal spasm
LaCl.	10.1	5.5	4.6	...	...	...	Hysteria; carpopedal spasm and extension of extremities
Bro.	9.5	4.2	5.3	...	...	...	Hysteria; carpopedal spasm; stiffness of extremities; also pelvic inflammatory disease

[*] All data are from the University of California hospitals except that from the medical service of Dr. Roland Cummings, the Los Angeles County General Hospital. (It is to be noted that the patient relapsed under large doses of viosterol.)

that is practicable for the clinical laboratory is the determination of the diffusible calcium fraction in the serum.[9] This fraction, although it is not completely ionized, contains the ionic calcium of the blood. There are many observations to indicate that the diffusible calcium can be used as a measure of the state of the physiologically available calcium in the blood stream.[10]

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9. Cameron and Moorhouse (J. Biol. Chem. **63**:687 [April] 1925) and recently Cantarow (Calcium Studies: Effect of Parathyroid Extract on Diffusibility of Calcium in Human Beings, Arch. Int. Med. **44**:834 [Dec.] 1929) objected to the determination of the diffusible calcium by the methods of ultrafiltration or compensation dialysis on the ground that artificial membranes cannot give the same distribution of constituents as that given by the living membranes of the capillary walls in the animal body. To avoid this objection, they proposed and used the calcium content of the spinal fluid as a measure of the true diffusible calcium in the blood. Accordingly, the former authors, working on parathyroidectomized dogs, concluded that the nondiffusible calcium disappeared in tetany, and the latter worker concluded that an increase in the nondiffusible fraction was responsible for the rise in the total amount of calcium after the injection of parathyroid extract in man. In each instance, they have arrived at conclusions opposite to the observations of the majority of observers employing ultrafiltration or compensation dialysis. The validity of the results of the aforementioned authors rests on the correctness of the view that at all times the amount of calcium in the spinal fluid represents the actual value of the diffusible calcium in the blood. The nondiffusible calcium in this work was obtained by subtracting the amount of calcium in the spinal fluid from the figures for the total amount of calcium in the serum. If the alterations in the calcium in the spinal fluid do not parallel the changes of the diffusible calcium in the blood, both in time and magnitude, as must necessarily be the case if the establishment of equilibrium between the blood and the spinal fluid lags, then the amount of calcium in the spinal fluid cannot be used as an index of the condition of the diffusible calcium in the blood and the deductions drawn by the aforementioned authors are false. One of us has recently presented evidence to show that the calcium in the spinal fluid is not continuously in equilibrium with that in the blood (Greenberg, D. M., and Ballard, H.: A Comparison of the Diffusible Calcium of the Serum and the Calcium of the Spinal Fluid, J. Biol. Chem. Proceedings **78**:65 [May] 1928. Greenberg, D. M. with the assistance of Ballard, H. E., and Dalton, J. B.: A Comparison of Ultrafilterable Serum Calcium and Cerebrospinal Fluid Calcium in Humans, Proc. Soc. Exper. Biol. & Med. **27**:514, 1930), and this view is supported by the recent work of Hertz (Biochem. Ztschr. **217**:337 [Jan.] 1930). The authors have further considered the objections against the employment of artificial membranes in another communication (Greenberg, D. M., and Gunther, L.: J. Biol. Chem. **85**: 491 [Jan.] 1930).

10. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, Physiol. Rev. **8**:283 (July) 1928; Studies in Calcium Metabolism: Calcium Content of Corpuscles, Plasma, and Serum, Biochem. J. **22**:548, 1928. Klinke, K.: Neuere Ergebnisse der Calcium forschung, Ergebn. d. Physiol. **26**:235, 1928. Gunther, L., and Greenberg, D. M.: The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

The micromethod of ultrafiltration, recently published by us[11] for the determination of the diffusible calcium in the blood serum offers a relatively simple practical method for the evaluation of the state of the calcium fractions in the blood and furnishes more useful data than can be obtained through the analyses of the total amount of calcium in the serum, plasma or whole blood. With this method, studies were made on parathyroid tetany, osteomalacia with tetany and tetany due to hyperventilation.

EXPERIMENTS ON PARATHYROID TETANY, JUVENILE TETANY AND OSTEOMALACIA WITH TETANY

Postoperative tetany developed in three patients, two women and one man who had undergone operations for subtotal removal of the thyroid gland. The detailed history of one case follows:

History.—I. F., an Italian woman, aged 33, entered the University of California Hospital on Feb. 1, 1926, complaining of an enlarged thyroid gland, prominence of the eyes, rapid pulse rate and palpitation of the heart. Twenty-three months prior to admission, she had been operated on in Switzerland because of these symptoms and signs. At the University of California Hospital, the diagnosis of multiple recurrent adenoma of the thyroid was made. The patient was operated on a second time on Feb. 13, 1926, in the surgical service, at which time a bilateral subtotal thyroidectomy was performed. On the day following the operation severe signs of tetany developed, as shown by the presence of carpopedal spasm and a bilaterally positive Chvostek sign. A diagnosis of postoperative parathyroid tetany was made. The total amount of calcium in the blood was 7.1 mg. per hundred cubic centimeters. The increased neuromuscular irritability was controlled by the combined therapy of 50 units of parathyroid extract-Collip by subcutaneous administration and 5 cc. of a 10 per cent solution of calcium chloride given by the intravenous route every six hours. Calcium salts were also administered by mouth. Eleven days after the operation she was discharged to the outpatient department, quite well, with instructions to take 15 Gm. of calcium lactate daily by mouth. The total amount of calcium in the blood on the day before discharge was 17 mg. per hundred cubic centimeters of serum. However, two days after discharge, the patient was readmitted with symptoms of tetany as before. The total amount of calcium was 8.7 mg. per cubic centimeter. Parathyroid extract-Collip was again administered in large initial doses that were gradually decreased over a period of eleven days, when she was again discharged to the outpatient department with instructions to take 2 Gm. of calcium lactate by mouth three times daily. There was 9.3 mg. per hundred cubic centimeters of calcium in the blood. During the period that she was followed in the outpatient department, the total amount of calcium varied around 8 mg. per hundred cubic centimeters, without outspoken clinical signs of tetany developing.

About a year after the first attack of tetany, the patient went through a normal pregnancy, and a congenitally rachitic infant was delivered at another hospital. The child was artificially fed and lived six months. On Aug. 8, 1928, slightly less than two and one-half years after the onset of tetany, the patient was readmitted

11. Greenberg, D. M., and Gunther, L.: On Determination of Diffusible and Non-Diffusible Calcium, J. Biol. Chem. **85**:491 (Jan.) 1930.

to the University of California Hospital with symptoms of tetany, and the total amount of calcium was 6.7 mg. per hundred cubic centimeters. Three months before this admission, a second child was born,[12] which she nursed. At the birth of the child she discontinued the large doses of calcium lactate (20 Gm. daily) that she had been accustomed to taking.

On a therapeutic regimen consisting of large doses of calcium lactate administered by mouth in divided doses, viosterol administered orally and parathyroid extract-Collip given subcutaneously, the total amount of calcium in the blood rose to 9.5 mg. per hundred cubic centimeters in eight days. The patient was again discharged on August 18, and seven days later she was readmitted with signs of tetany. Twenty units of parathyroid extract-Collip were administered subcutaneously that evening. The following morning the first specimen of blood was taken for study of the diffusible calcium. The signs of increased neuromuscular irritability were still present. The total amount of calcium was 6.3 mg. per hundred cubic centimeters and the diffusible calcium was 3 mg. per hundred cubic centimeters, the nondiffusible calcium by difference was 3.3 mg. per hundred cubic centimeters. After the administration of 50 units of parathyroid extract-Collip, the outspoken signs of tetany diminished, but the patient remained in a hyperirritable state. A second attack of tetany occurred in the hospital three days after admission (September 1). An analysis of the total amount of calcium at this time showed a value of 8.9 mg. per hundred cubic centimeters, the diffusible calcium was 3 mg. and the nondiffusible calcium 5.9 mg. per hundred cubic centimeters.[13] One and one-half months later, after the patient's discharge, convulsions appeared again, and clinical signs of tetany were present. The blood for analyses of the fractional calcium was taken within twelve hours of the convulsions, and showed a total amount of calcium of 9.5 mg. per hundred cubic centimeters, a diffusible calcium of 3 mg. and a nondiffusible calcium of 6.5 mg. per hundred cubic centimeters. When seen in the outpatient department, June 6, 1929, the patient seemed to be enjoying a fair degree of health, but she was still "nervous." At this time a physical examination showed that a questionable Chvostek sign was present. The analysis of the fractional calcium showed a total amount of calcium of 8.5 mg. per hundred cubic centimeters; the diffusible calcium was 4.2 mg. and the nondiffusible calcium 4.3 mg. per hundred cubic centimeters. The clinical condition was interpreted as possibly being latent tetany.

COMMENT

The observations are summarized in table 1. It can be seen that in patient I. F., in each instance, the diffusible calcium showed values between 3.3 and 3 mg. per hundred cubic centimeters of serum shortly after the onset of clinical tetany. During the entire period of active clinical tetany, the nondiffusible calcium varied between 3 and 6.9 mg. per hundred cubic centimeters. We have already noted that Cameron

12. After intensive treatment with cod liver oil, ultraviolet light and calcium, a sample of the child's blood at the age of 4 months showed a diffusible calcium of 4.3 mg. per hundred cubic centimeters. As will be pointed out later, there is good reason to believe that the diffusible calcium level of the infant was much lower at an earlier date. Diagnosis of congenital rickets was also made.

13. In this instance, while the diffusible calcium was still low, the nondiffusible calcium is well within the normal range.

and Moorhouse [14] arrived at the conclusion that in parathyropival tetany there is a reduction only in the nondiffusible calcium. This was also claimed by Cruickshank [15] prior to Cameron and Moorhouse. If this contention is correct, the nondiffusible calcium should have dropped to low figures during these active states, whereas in reality, the analyses showed that the nondiffusible calcium was within normal limits in two of the three analyses.[16] In the first analysis on patient I. F. and in the analyses on patients K. and S., the nondiffusible calcium also showed a decrease confirming the observations of von Meysenbug and McCann [17] and Moritz [18] that the nondiffusible as well as the diffusible calcium may show a decrease in tetany. But we cannot confirm their contention that the diffusible and nondiffusible calcium necessarily decrease in the same ratio. Our results are in conformity with those of Liu,[5] who reported similarly low values for the diffusible calcium in chronic juvenile tetany regardless of the state of the nondiffusible calcium. Likewise in his cases, clinical improvement did not follow the increase in the nondiffusible fraction of the serum calcium, but did follow the increase in the diffusible fraction.

The nondiffusible calcium, qualitatively at least, depends on the amount of the serum proteins,[19] and it may vary in such conditions as nephrosis without a concomitant variation in the diffusible calcium, as was first indirectly inferred by Salvesen and Linder [20] and recently by Peters and Eiserson.[21] We have observed in two cases of nephrosis at the University of California Hospital,[22] a decrease in the total amount of

14. Cameron and Moorhouse (footnote 9).

15. Cruickshank, E. W. H.: Studies in Experimental Tetany: Distribution of Calcium; Colloidal and Ionic Calcium, Brit. J. Exper. Path. **4**:213 (Aug.) 1923.

16. In normal persons we have found the extreme variation of between 4.1 and 7.4 mg. per hundred cubic centimeters for nondiffusible calcium and from 4.2 to 6.8 mg. per hundred cubic centimeters for diffusible calcium.

17. von Meysenbug, R., and McCann, G. F.: Diffusible Calcium of Blood Serum; Human Rickets and Experimental Dog Tetany, J. Biol. Chem. **47**:541 (Aug.) 1921.

18. Moritz, A. R.: Effect of Ultra-Violet Irradiation on State of Serum Calcium, J. Biol. Chem. **64**:81 (May) 1925; The State of Serum Calcium in Experimental Hypo- and Hyper-Calcemia, ibid. **66**:343 (Dec.) 1925.

19. Marrack, J., and Thacker, G.: State of Calcium in Body Fluids, Biochem. J. **20**:580, 1926. Loeb, R. F., and Nichols, E. G.: Factors Influencing Diffusibility of Calcium in Human Blood Serum, J. Biol. Chem. **72**:687 (April) 1927.

20. Salvesen, H. A., and Linder, G. C.: Inorganic Bases and Phosphates in Relation to Protein of Blood and Other Body Fluids in Bright's Disease and in Heart Failure, J. Biol. Chem. **58**:617 (Dec.) 1923; Relation Between Calcium and Protein of Serum in Tetany Due to Parathyroidectomy, ibid. **58**:635 (Dec.) 1923.

21. Peters, J. P., and Eiserson, Leo: The Influence of Protein and Inorganic Phosphorus on Serum Calcium, J. Biol. Chem. **84**:155, 1929.

22. This phenomenon, in nephrosis, has been further confirmed by one of us (L. G.) on further studies conducted on the Medical Services of Drs. W. H. Leake and V. R. Mason at the Los Angeles County General Hospital.

calcium, as a result of decrease in the nondiffusible calcium concomitant with low values for serum proteins. Liu has observed a decrease in the nondiffusible calcium for similar reasons in nephrosis and in kala-azar.[23] In these cases, as in cases of jaundice with low values for the total amount of calcium, in which there is also a decrease in the nondiffusible calcium,[24] no symptoms of tetany were observed. In the infant W, and in the adults with osteomalacia associated with tetany, at the time of convulsions, the diffusible calcium level was low, below 3.5 mg. per hundred cubic centimeters similar to that seen in the parathyroid tetany in patients I. F. and S. The diffusible calcium in the infant rose to 4.1 mg. per hundred cubic centimeters with alleviation of symptoms after five days of combined treatment with calcium chloride administered intravenously and cod liver oil administered by mouth. Liu [5] has shown that the combined administration of cod liver oil and calcium salts is the most effective means for relieving the symptoms of tetany.

TABLE 2.—*Studies Conducted at the University of California Hospital on Six Patients with Hyperthyroidism Showing a Tendency Toward a Higher Value for Diffusible Calcium*

Patient	Sex	Calcium, Mg. per 100 Cc.		Inorganic* Phosphate, Mg. per 100 Cc.	Serum Proteins, per Cent		Comment
		Total	Diffusible		Albumin	Globulin	
M.	Male	10.2	6.1	3.9	3.9	2.2	Hyperplasia
S.	Female	10.2	5.0	3.7	3.8	2.5	Hyperplasia
H.	Male	10.2	5.2	5.0	4.0	1.9	Hyperplasia
W.	Male	9.7	5.8	3.5	4.6	1.4	Adenoma
D.	Male	10.5	5.8	...	...	...	Hyperplasia
T.	Male	10.6	6.2	...	...	...	Hyperplasia

* All values in mg. per hundred cubic centimeters of serum.

In patient K., and likewise in patient S., the diffusible calcium estimated at the first appearance of subjective and objective symptoms, following the withdrawal of all treatment showed values of between 3.7 and 4 mg. per hundred cubic centimeters. Patient B., who was suffering from mild hyperplasia of the thyroid, and who showed a positive Hoffman sign, also had a diffusible calcium of 3.7 mg. per hundred cubic centimeters.[25] On the other hand in the group of patients with

23. Liu, Shih-hao: Partition of Serum Calcium into Diffusible and Nondiffusible Portions, Chinese J. Physiol. **1**:331 (July) 1927.

24. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, Arch. Int. Med. **45**:983 (June) 1930.

25. A low value for diffusible calcium was not the usual observation in hyperplasia of the thyroid. Studies conducted on six patients at the University of California Hospital (table 2) showed a tendency toward the higher zone for the normal values. A low diffusible calcium is more apt to be seen following a subtotal thyroidectomy in patients who are apparently not entirely relieved of the symptoms of "nervousness" or increased neuromuscular irritability and tremor. This is further shown by case S, from studies conducted at the Los Angeles County General Hospital.

miscellaneous muscle cramps, including hysteria and petit mal, and in the patients with tetany, I. F. and S., when they were clinically improved, the diffusible calcium levels were definitely above 4.2 mg. per hundred cubic centimeters.

It is evident that in the control of the neuromuscular irritability in juvenile and parathyroid tetany in which presumably the ionic calcium is important, the alterations of the diffusible calcium fraction of the serum that contains the ionic fraction is the significant observation. Our results in agreement with those of Liu [5] point to a value of about 3.5 mg. per hundred cubic centimeters or less of diffusible calcium as being associated with active manifestations of tetany, while possibly values between 4 and 3.5 mg. per hundred cubic centimeters may be associated with latent tetany.

The only recent work out of harmony with the conclusion that a low value for diffusible calcium is necessarily associated with the onset of tetany is that of Reed.[26] Working on parathyroidectomized dogs, he arrived at the conclusion that no relationship can be established between the incidence and severity of tetany and either the absolute amount or the percentage of diffusible calcium, and that the characteristic feature of prolonged parathyroid deficiency is the tendency to instability of both the diffusible and nondiffusible calcium fractions.[27]

Reed used the combined diffusion and ultrafiltration method of Moritz,[18] and we have elsewhere [11] pointed out that there is an element of doubt with this method because of the uncertainty that diffusion equilibrium is attained. Even so, a scrutiny of Reed's data shows that for three of his five dogs, namely, dogs 51, 52 and 56, the incidence and the severity of the tetany have a fairly high correlation with the drop in the value of the diffusible calcium. The data for the total amount of calcium presented by Reed bears out our contention that tetany may exist with values for the total amount of calcium remaining within the normal limits of variation.

TETANY DUE TO HYPERVENTILATION

It was pointed out in the introduction that attempts have been made to find either an alkaline shift in the acid-base balance or a lowering of the calcium ion concentration as the responsible factor in tetany, irrespec-

26. Reed, C. I.: On State of Plasma Calcium in Parathyroidectomized Dogs, J. Biol. Chem. **77**:547 (May) 1928.

27. It may be pointed out that all work up to the present on the relation between the severity of tetany and the distribution of calcium in the blood suffers from the defect that no exact measure of muscular hyperirritability has been applied, so that statements made on the severity of the tetany can have only a qualitative significance. In the future quantitative measurements of such a property as the chronaxie will be required to determine more strictly the exact relations.

tive of the origin. Although claims have been made that there is an alkaline shift in the acid-base balance in infantile and parathyroid tetany,[28] the experiments of recent workers, employing the improved modern methods, show no alkaline shift in the blood reaction. As examples, we may cite the work of Drucker and Faber [29] and Suzuki.[30] At the present time, the alkalosis theory of tetany in its application to tetany of juvenile and parathyroid origin may be considered to have been eliminated.

The theory that a reduction in the calcium ion concentration is responsible not only for infantile and parathyroid tetany, but also for tetany due to hyperventilation and an overdose of bicarbonate has become mainly associated with the names of Freudenberg and Gyorgy.[31] The essence of their theory is that increased alkalinity of the blood, increased inorganic blood phosphate or increased concentration of the bicarbonate ion produces a decrease in the ionic calcium without necessarily changing the total amount of calcium in the blood to any degree. This idea must further go back to the basis that the calcium ion concentration of the blood varies in accordance with some such formula as the Rona and Takahashi [32] equation. From this equation

$$Ca = K \times \left[\frac{C_H}{C_{HCO_3}}\right]$$

in which Ca is the calcium ion concentration, C_H is the hydrogen ion concentration and C_{HCO_3} the bicarbonate ion concentration, it is seen that a decrease in the hydrogen ion or an increase in bicarbonate ion should result in a decrease in ionized calcium. However, it is to be noted that the Rona and Takahashi equation is derived on the basis that the blood calcium is always at its saturation value, and that the adjustment to equilibrium is rapid. If these postulates are not true, i. e., if the blood calcium is at a level below saturation or if supersaturation can persist for considerable periods, then the application of the Rona and Takahashi formula or other formulas based on the same hypotheses have

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30. Suzuki, Kohji: Experimental Study on Alkalosis, Japan M. World **6**:108 (May) 1926.

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no validity. That the postulates on which the Rona and Takahashi equation is based are not valid is indicated by the work of Holt, La Mer and Chown [33] and Hastings, Murray and Sendroy [34] on the solubility of calcium salts in blood serum.

EXPERIMENTS

In considering how the calcium ion concentration of the blood might be reduced without a concomitant decrease in the total amount of calcium, the most reasonable view in tetany due to hyperventilation and an overdosage of bicarbonate is that as a result of the increased alkalinity the plasma proteins are able to combine with more of the calcium, forming unionized compounds. This would tend to keep the total amount of calcium high, even though the ionic calcium was being reduced. However, if this were true, a fractionating into the diffusible and nondiffusible calcium should show a decrease in diffusible calcium and an increase in nondiffusible calcium. To test this hypothesis, three experiments were carried out by us on tetany induced by voluntary hyperventilation. The results obtained are shown in table 3. The experiments were carried out on young normal adults, two females and one male, in much the same way as the similar experiments of Grant and Goldman.[2] A faster rate of breathing was employed than that used by Grant and Goldman, and tetany was thus induced in shorter periods of time.

The signs of tetany were observed in all three cases. Samples of the blood were drawn immediately before the experiment commenced and after definite symptoms of tetany were produced. The serum was analyzed for the total amount of carbon dioxide by the Van Slyke manometric method,[35] the p_H was determined by the Hastings-Sendroy colorimetric method,[36] and in a number of instances check determinations were carried out with the quinhydrone electrode. The total amount of calcium, diffusible calcium and inorganic phosphorus were determined by our previously described procedures.[11]

Table 3 shows that there was a definite alkaline shift in the blood reaction in all cases amounting on the average to nearly 0.2 of a p_H

33. Holt, L. E., Jr.: La Mer, V. K., and Chown, H. B.: Studies in Calcification: Solubility Product of Secondary and Tertiary Calcium Phosphate Under Various Conditions, J. Biol. Chem. **64**:509 (July) 1925.

34. Hastings, A. B.; Murray, C. D., and Sendroy, J., Jr.: Studies of Solubility of Calcium Salts: Solubility of Calcium Carbonate in Salt Solutions and Biological Fluids, J. Biol. Chem. **71**:723 (Feb.) 1927.

35. Van Slyke, D. D.; and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

36. Hastings, A. B., and Sendroy, J., Jr.: Studies of Acidosis; Colorimetric Determination of Blood p_H at Body Temperature Without Buffer Standards, J. Biol. Chem. **61**:695 (Oct.) 1922.

unit. We wish to emphasize, not the absolute values of the p_H but the relative shift. As the determinations in any one experiment were carried out at the same time under identical conditions, the shift in the p_H must be considered valid in spite of the objections recently raised against the colorimetric methods of determining blood p_H.[37] As an additional safeguard, we obtained agreement within the limits of the readings between the colorimetric method and the quinhydrone electrode in many check tests.

TABLE 3.—*Results Obtained in Experiments on Tetany Induced by Hyperventilation*

Subject	CO_2 Content, per Cent by Volume	Colorimetric p_H	Calcium, Mg. per 100 Cc.		Inorganic Phosphate, Mg. per 100 Cc.	Comment
			Total	Diffusible		
B. (female).....	....	....	....	....	....	Respiratory rate 36 per minute; symptoms: tightness across forehead and tingling in fingers and toes; spastic flexion of thumb and fingers of both hands; knee jerk reflexes hyperactive with increased spasticity of feet in extension; Chvostek sign negative
Before hyperventilation.....	56.5	7.53	9.85	5.70	3.70	
After 15 minutes hyperventilation	53.9	7.73	9.95	5.80	3.35	
T. (female).....	....	....	....	....	....	Respiratory rate 40 per minute; symptoms: spastic flexion of thumb and fingers of both hands; knee jerk reflexes hyperactive with increased spasticity of legs; Trousseau sign positive; Chvostek sign negative; Babinski sign negative; headache developed at conclusion of experiment
Before hyperventilation.....	62.0	7.45	10.6	5.35	4.85	
After 10 minutes hyperventilation	60.0	7.57	10.8	5.20	4.80	
G. (male).....	....	....	....	....	....	Respiratory rate 48 per minute; symptoms: tingling of fingers and tightness across forehead; spastic flexion of thumb and fingers of both hands; Trousseau positive; Chvostek sign slightly positive; Babinski sign negative
Before hyperventilation.....	70.8	7.35	9.95	4.90	3.15	
After 6 minutes hyperventilation	62.1	7.58	10.65	5.30	3.45	

The total amount of carbon dioxide in all cases shows a definite decrease. It is to be noted that, in conformity with other workers, we found a slight increase in the total amount of calcium, which probably may be attributed to a tendency toward dehydration in the blood. The significant observation is that the relation between the diffusible and nondiffusible calcium shows no alteration. The diffusible calcium is not at all decreased and even shows a slight increase. The experiments are definitely against the view that a reduction in the calcium ion concentration is a factor in tetany produced by an alkaline shift in the acid-base balance, namely, in tetany induced by hyperventilation and an overdosage of bicarbonate.

37. Myers, V. C., and Muntwyler, E.: Colormetric Estimation of Hydrogen Ion Concentration of Blood, J. Biol. Chem. **78**:243 (June) 1928.

SUMMARY

It has been pointed out that the analysis of the total amount of calcium in the serum is not a reliable guide to the state of muscular hyperirritability in juvenile and parathyroid tetany.

The determination of the diffusible calcium fraction in the serum offers a better criterion in such conditions. Our work and that of Liu point to a value of 3.5 mg. per hundred cubic centimeters or less of diffusible calcium as being associated with clinical symptoms of active tetany.

Tetany due to an alkaline shift in the acid-base balance, namely, tetany due to hyperventilation and an overdosage of bicarbonate, shows no decrease in the diffusible calcium, and is therefore probably not associated with a lowering of the concentration of ionic calcium.

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CORRECTION

In the article by Dr. Francis C. Wood, Dr. Charles C. Wolferth and Mary M. Livezey, entitled, "Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion," which appeared in the March issue (ARCH. INT. MED. **47**:339, 1931), Dr. Wood's address was given as New York. It should have been Philadelphia.

Book Reviews

ARTERIAL HYPERTENSION. By EDWARD J. STIEGLITZ, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago. Price, $5.50. Pp. 280, with 21 illustrations. New York: Paul B. Hoeber, Inc., 1930.

This book on hypertension represents a peculiar mixture of good and bad. It fills a certain need by its comprehensive review of the physiologic, pathologic and clinical concepts established as a result of the classic studies of Janeway, Allbutt and others. It contains a complete bibliography for the most part, and this is well indexed. Most of the general problems of hypertension are adequately discussed, although the interest of the reader is often dulled by the ponderous diction, the forced analogies and the unnecessary repetition. Certain deficiencies and omissions are conspicuous. Thus, the pathology of the retinal changes and even the ophthalmoscopic observations are dealt with poorly. There is no chapter on experimental hypertension. The chapter on renal reserve contains an unusual amount of extraneous material, including an unclear and none too critical discussion of the theories of the formation of urine. The most serious difficulties, however, are encountered in the chapters on etiology, treatment and prognosis. Under etiology, the author lists almost everything in the past history of his patients, including the excessive consumption of Worcestershire sauce (page 59). Loose statements are found concerning the relation of thyrotoxicosis, the calcium content of the blood and focal infections to hypertension. Is it really true or demonstrable that "the etiologic importance of focal infection can hardly be overemphasized" (page 69)? In discussing the treatment for hypertension by drugs, the author naively assumes that iodides can dissolve scars in blood vessels, thereby weakening them. He states that phenobarbital and bromides lowered the blood pressure in from 85 to 88 per cent of cases, but curiously omits the corresponding statistics for his own favorite drug, bismuth subnitrate (page 138). The chapter on prognosis illustrates how difficult it is for the medical mind to view therapeutic results without shutting the critical eye. In spite of these weaknesses, the book will be of considerable value to those interested in arterial hypertension. Since this is the first edition, there is opportunity for later improvement.

INSULINTHERAPIE. By E. FRANK, M.D., and A. WAGNER, M.D., Physicians of the Wenzel-Hancke Hospital, Breslau. Paper. Price, 8 marks. Pp. 99. Leipzig: Georg Thieme, 1930.

This little book opens with a concise historical sketch of the scientific work, from von Mehring and Minkowski to Banting and Collip, that led to the discovery and isolation of insulin. This is followed by a short discussion of the theories of the action of insulin and then by a practical exposition of the treatment for diabetes and its complications. Other chapters cover insulin therapy in the diabetes of children, resistance to insulin and complications attending the administration of insulin, especially the hypoglycemic reaction and edema caused by insulin. In a second section, critical consideration is given to the use of insulin in nondiabetic diseases, especally in cachexia and anorhexia, in parenchymatous lesions of the liver, in hyperthyroidism, in infections and in other conditions. While the reviewer, from personal experience, is inclined to be somewhat more critical than the author as to the value of insulin in nondiabetic diseases, he nevertheless finds the book of great interest, and recommends it highly as a working guide for the use of insulin in diabetes and its complications.

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